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THE MANY-SIDED PUSEY

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AT THE outset I wish to express my appreciation of the honor of being one of those to speak at the second annual William Allen Pusey dinner. It is a privilege that I welcome, for it provides an opportunity to pay personal tribute to a friend of many years who had the warm regard of all of us and of whom I am sure that we will all continue to think kindly. Although Dr. Pusey became one of the eminent men of American dermatology and had risen also to the heights in American medicine—all by virtue of a long career of useful accomplishment and service—the Chicago Dermatological Society ever remained "home" to him and claimed a special and sentimental interest. This dinner again gives expression to Dr. Pusey's firm belief in the value of what he considered to be one of the important functions of our society—"the promotion of friendship and good understanding among its members." I am sure that you will agree that in furthering this objective the Pusey dinners under Dr. Mitchell's capable direction will all be most successful.

At the first annual dinner a year ago some of the varied activities of Dr. Pusey's busy life and of his personal attributes were related by Dr. Oliver, Dr. Brown Pusey, Dr. Senear, Dr. Rattner and Dr. Weber. On a previous occasion, ten years ago, when Dr. Pusey, at the age of 71, had resigned as Editor of the ARCHIVES, Dr. Rattner gave a most interestingly written account of Dr. Pusey's life and accomplishments. This was published in the ARCHIVES under the title of "William Allen Pusey at Close Range," and should be read and read again by every dermatologist.[1] It is a delightful biographic sketch, which gives an excellent and lively portrayal of Dr. Pusey as he lived and worked among us. Thus, many aspects of Pusey's life have been heretofore portrayed for us, and my remarks will be more in the nature of reminiscences, largely of earlier days, now seen in retrospect

Read at the second annual William Allen Pusey dinner of the Chicago Dermatological Society, Chicago, Oct. 15, 1947.

1. Rattner, H.: William Allen Pusey at Close Range, Arch. Dermat. & Syph. 35:25-66 (Jan.) 1937.

with the hypermetropic eye of an old friend, and which I hope will add some brush strokes to the portrait.

My acquaintance with Dr. Pusey began in 1903 by reason of a common interest in roentgen therapy, especially for dermatologic conditions and malignant growths. At that time Dr. Pusey, then 38 years of age, with about four years of pioneer experience, was already recognized as a leading authority in this country in the new and only partly explored field. Within this short time he had gathered sufficient material and enough experience to publish several papers containing clinical and technical information of fundamental importance. A wave of uncontrolled and uncritical enthusiasm about roentgen therapy and diagnosis was spreading over the country at the time, paralleled a few years later by a similar wave when arsphenamine was introduced for the treatment of syphilis. In contrast to some others of this period, Pusey's reports were conservative and factual and showed restrained and sound judgment which established confidence, and, therefore, his reports were influential in establishing basic principles. His book on roentgen rays in treatment and diagnosis, written in collaboration with Dr. Eugene Caldwell of New York and published in 1903, was an authoritative pioneer effort in this field and remained a standard treatise for years.[2]

I speak of the events of this period with special detail because I, too, believe, as Rattner has said, that the pioneer work done by Pusey in roentgen therapy "was the most important, perhaps the decisive, factor in establishing him as a national figure in medicine." Later he restricted his work more and more to treatment of dermatologic disease with roentgen rays, as the development of equipment and technics for high voltage and massive therapy increasingly required specialization in a field removed from dermatology, for dermatology throughout had remained Pusey's chief interest.

The x-ray apparatus in use at this early period was primitive and bore about the same comparative relation to modern equipment as the first automobiles, with their adapted horse-drawn carriage design, rear entrance, buggy top and bag for golf sticks and umbrellas, bear to the present streamlined luxury cars. The induction coil with mercury turbine interrupter provided the current for the tube, which provided a quality of ray depending largely on the degree of vacuum. The quality of ray was judged by the kind of bone shadow shown on a barium-platino-cyanide screen in a hooded box, originally held by hand before the eyes. Dosage was a matter of individual judgment and could not be accurately expressed and defined nor

2. Pusey, W. A.: Roentgen Rays in Therapeutics and Diagnosis, Philadelphia, W. B. Saunders Company, 1903.

transmitted to others. This accounted for many of the early overexposures and tragic consequences, until other devices for gaging x-ray quality and output were gradually developed. It brought about the use of lead and rubber sheeting and gloves for the protection of both patient and physician, lead foil and plates for insulation of treatment rooms and hoods for open tubes.

Throughout this period Pusey and other conservative workers preached caution and warned of the dangers attending the use of this powerful agent. In view of what is known today about roentgen rays and considering the comparatively primitive means available in the early nineteen hundreds, it is remarkable that even in the hands of capable men such good results were obtained and that so little damage was unknowingly produced.

During 1903 and 1904 I made frequent trips to Chicago, and, at Dr. Pusey's open invitation to come in for a chat when possible, often spent a half-hour or longer with him in the late afternoon—visits that usually ended in the dim light of a quiet immaculate nearby bar where one Manhattan was imbibed with proper ceremony. After this Pusey would put on his inevitable gray cloth gloves and go to look for Richard, the chauffeur, and the Haynes car, parked somewhere nearby.

Our talks were at first chiefly concerned with roentgen rays, with which I had some short experience, as an intern in 1899, in Vienna in 1900 and later at home, and we often discussed the problems of dosage and injuries due to roentgen rays and their prevention. He was interested in everything he could read or hear on these subjects and had an original system of filing clippings and notes in a large manila envelope carried in his coat pocket, to be retrieved for study later in the evening. I was impressed by the deliberate consideration he gave to every question before passing judgment. Deliberation was characteristic of Pusey, and, as I learned later, he never seemed to undertake or do anything on impulse, but only according to plan, and, as he said, "common sense." His deliberate nature was expressed even by his walk and in his stocky build. He was a good questioner and did not leave a debatable subject until it had been fully discussed and was clear in his mind. This was in accord with his ability so often displayed at our meetings to attack a perplexing situation or problem, reduce it to its elemental components and show that the solution was, after all, a simple and logical matter.

I well recall that on my first visit at Pusey's office I was impressed with the practical character of everything in and about it, including the physician, who seemed somewhat dwarfed by the size of his shining black leather swivel chair in front of the solid-looking roll-top desk, which appeared somehow to complement and be a part of him.

Later I saw that Pusey was eminently practical, perhaps because of early training by his father, a country physician of the old school. Rather than wait for a nurse, I have often seen him deftly apply dressings and bandages himself or apply what he called an ointment patch, demonstrating that a properly applied dressing is an important part of local treatment.

When I last saw the old desk and chair, five years ago, in the Brown Pusey house at Elizabethtown, Ky., where Dr. Pusey's memorabilia are now installed and preserved, I could look back through the years and again see Dr. Pusey, just as Dr. Rattner many years later records having seen him still unchanged—tilted back in the large chair, legs swinging, spectacles perched high on his forehead and flicking the ashes of a little VanBibber cigar over his shoulder into an old apothecary's mortar perched on a stand somewhere behind him. However, my memory picture was that of a more youthful Pusey, with clearcut, calm and intellectual features, and it recalled the time when I once remarked to him that he should include a picture of Benjamin Franklin among those on his walls, because in many ways he resembled Franklin. He frowned as though displeased, looked at me sharply and snapped, "What makes you say that?" I replied, "Because I think you do." A quizzical expression slowly replaced the frown as he chuckled and said, half embarrassed, "Foerster, I consider that a real compliment, for I am very fond of Franklin as one of the most useful of all Americans." It then developed that, like myself, he had for a long time cultivated an interest in Franklin and had read and gathered Franklin material as a minor hobby or interest, without telling any one about it. Thereafter, whenever I came across something on Franklin which I thought would interest Pusey I sent it to him and always enjoyed receiving his acknowledgment, which usually was one of his scrawled, often humorous, quips or notes.

I like to think of Pusey as the Benjamin Franklin of dermatology —a many-sided practical man who made useful and important contributions not only in his field of specialized practice, teaching and literature but beyond that in organized medicine, public health, education and civic service and who reached the heights in both fields. Pusey gave prestige to dermatology as its able ambassador in the high councils of medicine and of public service.

Pusey was a delightful traveling companion; well supplied with his little cigars, he was relaxed, witty and fond of light or earnest discussion, as the moment required. When meals were announced he made a game of matching coins to see who was to pay for the cocktails and who for the meals, and if he won both he chuckled heartily. Usually the score was about even when the trip ended. The simple

pleasure he derived from winning at matching coins and the satisfaction of making a series of good shots at billiards, at which game he was fairly expert, were far surpassed, however, by the joy of holing a long putt on a difficult green. I have seen him make such putts on our home course and heard him happily recount the exact details seven or eight years later.

I never heard Pusey discuss personalities, and he disliked gossip. He was intolerant of deceit, and, though he usually restrained his temper even when provoked in debate, he could express his mind in no uncertain terms when the occasion demanded it, especially when others evaded or shirked the issue. I was present with Dr. Grover Wende on one such occasion in St. Louis, when, after the meeting was ended, Pusey sought out and thoroughly denounced one of the members as a fraud. I recall one incident, however, in which Pusey came out second best in a dispute. Some of the members will recall the battle of the Masonic Temple when this society, despite the belligerent vocal objections of Dr. Pusey, was ejected from the meeting hall by the janitor on the stroke of five, before the meeting was ended, by the simple process of sweeping the floor and removing the chairs. This occurred long before the Wagner bill was enacted.

Pusey was forthright in speech, left no doubt as to his views, seldom failed to express them and often made his point stick with an apt or witty comment. This forthrightness led to a certain incident with an important sequel, of which I was told and which I have no reason not to believe. Shortly before our entry into World War I, a national meeting of public health and social workers of the "do-good-er" type, including a number of physicians, was held in Washington, D.C., for the purpose of discussing measures to control what they called "social diseases" in the event of war. Pusey, who had recently published a monograph, "Syphilis as a Modern Problem,"[3] heard of the meeting and decided to attend and listen, though apparently he had not been invited. The indecisive, futile and inept manner in which the subject was approached and discussed aroused Pusey's indignation to such an extent that he could no longer contain himself. He asked for the privilege of the floor, confronted the audience and began a forthright attack on their proceedings by shouting, "You are not here to discuss the Lord's prayer, but to prepare to fight the vicious diseases called syphilis, gonorrhea and chancroid," and he continued in a similar vein. It happened that Dr. William Welch of Baltimore, a powerful and trusted leader in medicine and highly influential in Washington, also had come to the

3. Pusey, W. A.: Syphilis as a Modern Problem, Chicago, American Medical Association, 1915.

meeting uninvited to listen and observe and watched the proceedings unnoticed. He was impressed by Pusey's earnest attack and evident grasp of the subject and made further inquiries, and it was not long before Pusey was summoned to Washington by the Surgeon General of the Army. He was there invited to form and head the Surgeon General's Advisory Committee of five men for handling the problems of syphilis and venereal and cutaneous diseases in the Army in the United States during the World War.

This is the story as it was related to me, and, whether true in every particular or not, it had a good ending. Pusey, then 52 years of age, accepted what he called "that appalling responsibility" and was given a free hand. From the middle of July 1917 until after the end of the war, he put all his great capacity for work into the direction of this tremendous task, which he and his committee completed with distinction.

Pusey's unusual capacity for productive work and intelligent executive direction was shown also by his successful career as Editor of the ARCHIVES for a period of sixteen years. He had a decided literary bent, shown early in life, had a critical sense of values and was fair minded, and the work of an editor was a natural avocation for him. His conscientious work has left its impression on American dermatologic literature and made the ARCHIVES one of the foremost journals in our special field.

Pusey was an approachable and friendly man, with little outward show of emotion, but like many such persons he had deep sentiment and affections. Our presence here is evidence of that. His closest friends in dermatology were Grover Wende and Milton Hartzell, both plain men of strong character, serious minded but with a jovial lighter side. They were an inseparable trio at all national meetings for at least twenty-five years and were often joined by John Fordyce. All had a common interest in clinical and microscopic dermatologic photography, which was then in the process of development. For many years their work was outstanding, and some of it has not been excelled to this day. Pusey always claimed that Grover Wende was one of the three most skilful photographers in America, and, perhaps, that estimate may still hold good.

Many of you probably will recall a bit of friendly pleasantry of which Pusey was fond. I refer to his invitation, usually accompanied with the Pusey chuckle, to sit beside him in the front row of seats and "join the elder statesmen." He was in fact an elder statesman even when he was still young in years, for Pusey had reached maturity of mind earlier than most because he had to accept responsibilities early. It becomes evident from his writings that he had thought much about the true values in life and had early determined for himself

a philosophy by which he would be guided. It is based on usefulness in life. In everything Pusey has written, including some of his medical works, the word "useful" appears repeatedly and prominently, and he used it often when speaking. In fact, in his delightful "October Views in Medicine," much in the essay is concerned with "usefulness" and its opposite "uselessness."[4] He was much in earnest about usefulness. In the memorial address that Pusey wrote twenty years ago for his intimate friend Dr. Grover Wende, he stated that if one's early experience in life trains one to an interest in its real problems and to distinguish between the essentials and unessentials, if one's unconscious guide is usefulness and if one finds a useful intellectual vocation, one can ask no better lot. Perhaps Pusey unconsciously was thinking also of himself when he wrote this.

Pusey attained the heights in organized medicine when he was elected President of the American Medical Association at San Francisco in 1923. I remember it well, for I met Pusey browsing around by himself in the hall of scientific exhibits, minus his cane, that morning. We spent a long time viewing the exhibit on tularemia, then a new disease unknown to us, and talked about its possible importance to dermatology. Presently Pusey looked at his watch and said that he was expected on the upper floor where the delegates were in session, because he was told that he had been made president-elect, and said that he wished that I would go to the meeting with him. John Lane of New Haven met us in the deserted corridor, and we waited, walking slowly back and forth. Pusey was composed and serious, spoke of the great demands made by the office and said that he was certain that he could meet them and that he would be the second member of his family to be so highly honored. After a time he turned to me and said with a characteristic chuckle, "Foerster, I believe that you and Lane are more nervous about this than I am," and he was right, for I was bathed in perspiration from the suspense and strain of waiting, which seemed to affect him little. Just then the door was opened, and as Pusey entered the hall a roar of applause greeted him from the standing House of Delegates. He squared his shoulders, looked straight ahead, and, as I watched from the doorway, I saw Dr. Pusey, one of our own, of whom we will always think kindly, walk sturdily forward to assume still another task of useful service and to receive the highest honor the united medical profession of our country can bestow.

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4. Pusey, W. A.: October Views in Medicine, A.M.A. Bull **24**:36 (Feb.) 1929.

TUMORS OF THE TESTICLE WITH DERMATOLOGIC SEQUELAE

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TWO CASES are herein reported on; the first is an addition to the record of a rare condition, malignant metastases in the skin from the testicle, and the second is of a dermatologic condition associated with malignant disease of the testicle, which is intriguing and justifies speculation.

REPORT OF CASES

CASE 1.—An American soldier, white, aged 24, and married (no children), while on Pacific duty, about January 1944, noted a gradual enlargement of the left testicle and six months later noticed vague and intermittent aching in the left side of the scrotum. Two months later this same testicle was accidentally injured. This was followed by episodes of severe pain in increasing frequency. On December 4, an orchidectomy was done, and a diagnosis of embryonal carcinoma of the left testicle was made. The patient was then transferred back to the United States for continued treatment. He entered the hospital on June 9, 1945.

Past History—The family history was not contributory. His past history indicated a possible renal infection during childhood. He had had a tonsillectomy when he was 7 years old. In May 1942, he had undergone ligation of the saphenous veins for varicosities.

Physical Examination on Admission—The patient was 72 inches (about 183 cm.) tall and weighed 145 pounds (about 66 Kg.). (His normal weight was 160 pounds (about 73 Kg.). The skin was clear with the exception of a few comedos, papules and pustules on the shoulders. There were bilateral inguinal scars which marked the site of the saphenous ligation. There was a well healed scar on the anterior aspect of the left side of the scrotum. The lymph nodes in the left axilla were definitely enlarged, one of them being at least 1 inch (about 2.5 cm.) in diameter. There were some firm slightly enlarged lymph nodes in the left inguinal region.

Laboratory Observations.—The white blood cell count was 15,200; the hemoglobin content was 14.7 Gm. A smear of the blood showed: neutrophils 69, lymphocytes 26 and monocytes 5. The sedimentation rate was 5 mm. in one hour. The level of the blood phosphorus was 3.6 mg., and the alkaline phosphatase was 5.2. The cholionic gonadotropin titer (Powell method) was 3,000 mouse units per liter of urine.

During the course in the hospital the sedimentation rate gradually increased, and on Feb. 20, 1945, it was 59 mm. in one hour. Other elements of the blood showed the following changes on March 14: red blood cells 3,720,000, white blood

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cells 7,000 and hemoglobin 10.8 Gm. A roentgenogram of the chest on January 13 showed extensive pulmonary metastasis. Retrograde pyelography showed lateral displacement of both ureters, suggesting bilateral perihilar lymph node metastasis. Subsequent roentgenograms of the chest revealed an increase in the number and size of the metastatic lesions in the chest.

Course in the Hospital.—Palliative roentgen therapy was administered in the form of 1200 r (air) to each of four ports covering the pulmonary field. This was poorly tolerated. Within a short time the patient began to cough up varying amounts of blood. Early in February, a small tender nodule appeared in the region of the thyroid. This increased in size until it was about 1 inch (about 2.5 cm.) in diameter. Early in March the patient began to have difficulty breathing and moving, and at this time the nodules in the skin appeared. There were some in the scalp, one was in the left side of the abdominal wall, one just below the right inguinal fold and one on the right calf. They were firm bluish nodules about the size of a small cherry, and they were freely movable. The course of the disease was one of gradual down-hill progression. On March 25, following a convulsive seizure, the patient died.

Postmortem Observations.—The tumor in this case was uniform throughout. The various nodules were round and composed of rather large cells. These cells encircled large areas of necrosis. The necrotic areas appeared to be made up of granular eosinophilic materials, containing necrotic debris and areas of hemorrhage. The tumor cells were of two types. The one which predominated was a large cell with an enormous vesicular nucleus containing a central nucleus. The cytoplasm was abundant and basophilic. The cells were massed in solid sheets and considerable mitotic activity was present. The second cell was probably derived from the former by amitotic division. The nuclei were hyperchromatic and pyknotic. There was considerable variation in size and shape. In general this tumor presented the characteristic features of a malignant chorioma.

Comment.—We feel justified in reporting this case inasmuch as in the papers of Gates[1] and, more recently, Beerman and associates[2], which deal with cutaneous metastases, no mention is made of metastases from the testicle. However, Rothmund[3] of Germany has reported such a case.

Case 2.—A white soldier, aged 32, was admitted to the hospital Feb. 18, 1945.

History of Present Illness.—In October 1944, while on Pacific duty, the patient noted plugging of the pores of his nose, which made it feel like the bristles of a brush. Within a few weeks, in spite of treatment, the skin of a good portion of the upper aspect of the trunk was similarly involved. Various diagnoses were considered, such as vitamin A deficiency and lichen pilaris, but there was no response to vitamin A therapy, in spite of the fact that 50,000 units were taken daily for a period of three weeks. On Jan. 6, 1945, the patient was admitted to a station hospital, and at that time he noted considerable loss of hair of the scalp, arms and eyebrows. A tumor of the right testicle was noted early in February. Further questioning elicited the following information: In 1932 the patient was kicked in the testicle and there was swelling of one week's duration. He had no further difficulty. Approximately four years ago, during a routine examination, he was told that his right testicle was atrophic. He had no complaint at any time in regard to the testicle, and the fact that he had an enlargement was brought to his attention during a physical examination early in February 1945. It should be noted that six

1. Gates, O.: Am. J. Cancer **30**:718 (Aug.) 1937.
2. Beerman, H., and others: Am. J. M. Sc. **212**:479 (Oct.) 1946.
3. Rothmund, K.: Deutsche Ztschr. f. Chir. **253**:513 (Sept.) 1940.

months prior to his admission to the hospital, this patient had been complaining of frequent nocturnal emissions. Results of physical examination were essentially negative except for an enlarged right testicle. It was enlarged approximately one and a half times. There was a sparseness of the hair of the scalp, and the eyebrows were somewhat thin. There were a number of follicular comedo-like lesions involving the butterfly region and the regions just anterior to the auditory canals. There were also similar lesions on the chest, above the waist and extending onto the forearms. Some of those on the chest and back were inflammatory papules, not unlike those seen in acne vulgaris. The laboratory observations were essentially normal, or well within normal limits.

Course in the Hospital.—After a complete evaluation, which indicated no metastatic lesions, it was decided to give this patient preoperative and postoperative irradiation to the right testicle. On April 6, the right testicle was removed, and histologic examination revealed an embryonal carcinoma of the seminoma type. The course of the disease was uneventful throughout the patient's stay in the hospital except that, following high voltage roentgen therapy to the inguinal nodes and paravertebral nodes, some diarrhea ensued. The unusual aspect in this case was the development of typical lesions of cystic acne late in March and early in April, and the complaint of nocturnal emissions was again registered by the patient early in May. About this time the course of high voltage roentgen therapy was completed, and the patient was not seen for a period of approximately thirty days. On his return from a visit to his home after the middle of July, the acne-like lesions had considerably cleared, with general improvement of the cutaneous condition.

COMMENT

We feel it conservative to say that there was an obvious connection between the dermatologic symptoms and the testicular disease, largely because of the improvement following treatment with roentgen rays and surgical intervention.

Two ideas suggest themselves:

1. Excess androgen was stimulated by the tumor process, and this is relieved by treatment with roentgen rays and surgical intervention. There is not much evidence to support this thesis. It is known that seminomas frequently excrete gonadotropin, which may possibly be a factor. Twombly[4] referred to the work of Hamburger, who observed decreased androgen after excision and who suggested that this might release the pituitary. Hamilton,[5] in 1941, discussed the male hormone in acne and concluded that there was a stimulating affect on the sebaceous system, particularly around the nose. He was able to produce acne-like lesions in eunuchs by injecting testosterone propionate. His work was confirmed by Rony and Zakon,[6] who were able to increase the size and activity of the sebaceous glands by administration

4. Twombly, G. H.: Surgery **16**:181 (Aug.) 1944.

5. Hamilton, J. B.: J. Clin. Endocrinol. **1**:570 (July) 1941.

6. Rony, H. R., and Zakon, S. J.: Effect of Endocrine Substances on Adult Human Scalp, Arch. Dermat. & Syph. **52**:323 (Nov.-Dec.) 1945.

of testosterone propionate. Hamilton[7] further, in 1942, mentioned the loss of hair following the administration of male hormone in eunuchs. In this case the loss of hair was a marked symptom.

2. Did the roentgen rays directed to the testicular area have an effect further afield? Niles[8] reported improvement of acne on the opposite cheek when only one cheek was directly treated with roentgen rays, and it has been reported that ultraviolet radiation affects areas not exposed to the rays. However, the effect of oversupply and lessening of the amount of the hormones seems the likeliest factor.

17 East Grace Street.

ABSTRACT OF DISCUSSION

DR. MAURICE SULLIVAN, Baltimore: Rothman (Skin Manifestations in Malignant Tumors of Internal Organs, *Arch. f. Dermat. u. Syph.* **149**:99, 1925), classified cutaneous disturbances accompanying malignant tumors of internal organs into four groups: (1) pruritus and a prurigo-like syndrome with hyperpigmentation, (2) toxic bullous eruptions, (3) metastatic cutaneous lesions and inflammatory lesions preceding metastases and (4) acanthosis nigricans and similar proliferative changes. Later Becker, Kahn and Rothman (Cutaneous Manifestations of Internal Malignant Tumors, ARCH. DERMAT. & SYPH. **45**:1069-1080 [June] 1942) surveyed the literature on the cutaneous manifestation of internal malignant tumors and reported on 2 illustrative cases. They suggested that carcinoma cells might be destroyed in the skin by cutaneous defense mechanisms and that the clinical manifestations of the defense reaction might be either necrosis or inflammation. It is apparent that the location of the tumor influences the type of cutaneous alterations, as impairment of the function of the implicated organ is likely to reflect itself in disturbed function related to the organ. In 1 of the cases of Becker, Kahn and Rothman, there was a tumor of the pancreas, with resulting disturbance of carbohydrate metabolism and complicating monilial infection. It is conceivable that, if searched for, a variety of dermatoses may be added to Rothman's original classification and that the range of types of cutaneous manifestations is considerable. Cachexia and poor nutritional status of tissues in patients with malignant tumors also contribute to lack of integrity of the skin and its failure to withstand infection as well as degenerative changes and inflammatory changes due to many mechanisms. Urbach (Endogenous Allergy, ARCH. DERMAT. & SYPH. **45**:697-722 [April] 1942), in discussing the complex proposition of hormonal endogenous allergy, involving the question of menotoxin, reported the occurrence in a woman of severe dermatitis dysmenorrheica which underwent involution following temporary roentgen ray sterilization. When ovarian or testicular tumors are considered, the possible cutaneous changes are numerous, as the state of the skin is influenced in many ways by estrogens and androgens, particularly in regard to acneform eruptions and hair growth. Twombly (Relationship of Hormones to Testicular Tumors, *Surgery* **16**:181-193 [Aug.] 1944) pointed out that the following facts about teratoma testis suggest endocrine causation: (1) the frequent occurrence of teratoma in patients suffering from cryptorchidism or pseudohermaphroditism, (2) the high

7. Hamilton, J. B.: Am. J. Anat. **71**:451 (Nov.) 1942.

8. Niles, H. D.: Roentgen Rays in Treatment of Acne: Evidence That They Do Not Produce Scarring, Arch. Dermat. & Syph. **27**:89 (Jan.) 1933.

incidence of this type of tumor during the period of greatest sexual activity and (3) the observation of high levels of castrate type of gonadotropin, follicle-stimulating hormone, and low levels of androgenic hormone in urine with testicular cancer, particularly seminoma. In the authors' second case, the relationship between the cutaneous changes probably due to endocrine factors, which subsided after roentgen irradiation, introduces another type of cutaneous lesion which should be included in the category of cutaneous manifestation of malignant tumors. The evidence for the relationship is in the realm of speculation, but the chances are that similar circumstances may arise again in the case of another radiosensitive seminoma to confirm the contention of Dr. Murrell and Dr. Pepple. It would be interesting, also, to determine whether there are similar cutaneous manifestations in patients with dysgerminomas.

DR. HOWARD HAILEY, Atlanta, Ga.: The paper of Dr. Murrell and Dr. Pepple is a stimulating one, and I predict that the seeds have been sown for future investigation.

I want to mention two instances of interest in members of the canine family. The first was the case of a fine bird dog that had generalized eczema which failed to respond to treatment. Finally, 5 grains (0.3 gm.) of morphine were given hypodermatically. The dog crawled under a house and came out three days later, entirely well.

The second instance is that of another dog with generalized eczema. I had observed this dog for a period. A tumor of the testicle developed and was operated on. After the operation, the eczema disappeared promptly, without any treatment.

DR. MAURICE J. COSTELLO, New York: Aside from the rare dermatologic manifestations of testicular tumors, I should like to make a plea to physicians to refer young men presenting an undescended or atrophied testicle, the forerunners of testicular tumors, to the genitourinary surgeon for proper appraisal of the significance of these observations.

These tumors occur with a degree of frequency in physicians, and, according to the late Dr. James Ewing, 38 is the commonest age for their appearance.

THERAPEUTIC VALUE OF AMMONIACAL SILVER NITRATE IN FUNGOUS INFECTIONS OF THE NAILS

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FUNGOUS infection of the nails, or onychomycosis, is more frequent than has been suspected in the past. The anatomic structure of the nail, with its high content of keratin, provides a good location for the development of certain of the pathogenic fungi. The thickness of the nail tissue and its comparative impermeability cause infections of the nails to be among the most resistant to treatment of the superficial mycoses.

The organism responsible may be Candida albicans or one of the species of dermatophytes, such as Trichophyton rubrum or Epidermophyton floccosum; mixed infections are apparently uncommon in this particular type of disease. The invading fungus penetrates the nail along the free edge and grows toward the matrix, gradually infecting the entire nail and the nail bed and may involve the matrix itself. The nail becomes discolored and turns dirty yellow or brown, losing its luster and presenting a dull uneven surface with many ridges and depressions. The consistency of the nail is decidedly altered, with various degrees of friability observable. There is often severe subungual thickening. The nail may be raised from its bed, either at the free margin or along the entire nail bed. The anterior portion, or the entire nail, may be freed entirely and cast off. There is usually no noticeable inflammatory reaction and no paronychial involvement in nail infections caused by dermatophytes. In infection with Candida organisms there may be some paronychia, with erythema, swelling and some pus exuding along the lateral margins of the nail bed and even under the lunula; C. albicans can be isolated in culture from the pus.

Diagnosis of these infections is a laboratory procedure. Specimens of pus or nail scrapings are allowed to disintegrate in strong potassium

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hydroxide. Under subdued light and with a narrowed diaphragm opening, yeastlike cells and/or mycelial elements may be detected microscopically. For identification of species, isolation of the fungus in culture is necessary.

Results of treatment of onychomycosis have been disappointing. Almost every conceivable medicament or method of treatment has been tried. The list includes: ordinary iodine, methylrosaniline chloride, potassium permanganate, benzoic and salicylic acid ointment, sodium perborate paste, chrysarobin, ammoniated mercury, acetic acid, sodium thiosulfate, Fehling's solution, cupric sulfate and potassium hydroxide. Other methods of treatment include: autogenous and stock vaccine, dry heat up to 300 to 400 F., iodine inhalations, roentgen rays and surgical removal of infected nails. Recurrences following surgical removal are by no means uncommon; removal of nail tissue with dental burrs has been somewhat more satisfactory. In general, all types of treatment have proved unsatisfactory.

While conducting some experimental work on the physiologic aspects of pathogenic fungi, one of us[2] (W.J.N.) conceived the idea that the problem might be solved by the use of a substance that was fungicidal and which also could penetrate keratin. After some study, such a substance was found in ammoniacal silver nitrate. This complex silver salt has the property of penetrating keratins generally, and nail tissue in particular, to a high degree.

Preliminary experiments with ammoniacal silver nitrate were carried out with laboratory animals which had been infected from cultures of certain of the dermatophytes. Animals used were the white rat and the guinea pig. They were inoculated after being anesthetized, by sandpapering a closely clipped area and applying a suspension of spores and mycelia (made up in sterile distilled water from a vigorous culture) with a sterile swab. Localized lesions developed within a week to ten days at the site of inoculation; the lesions tended to clear spontaneously about one month after first appearing. A thin film of ammoniacal silver nitrate was spread over the inoculated site immediately following inoculation, and no lesions deveoped. The compound was evidently fungicidal for the spores and mycelia in the inoculum. When treatment was delayed until after the appearance of a lesion, the infection was observed to clear within about one week after a single application of ammoniacal silver nitrate as a thin film over the entire lesion; that is, clearing of the lesion occurred about three weeks sooner on the average than it would have spontaneously. No untoward reactions were observed in the animals as a result of the treatment. However, when the site of a lesion treated with ammoniacal silver nitrate was maintained artificially at a humidity near saturation,

with the aid of small plastic shells placed over the site, it was observed that untoward weeping and exudation from the lesion occurred. While not definite, we interpreted this to contraindicate the use of ammoniacal silver nitrate for moist or weeping lesions, such as lesions between toes and in cases of accompanying hyperhidrosis. It was noted early in this preliminary work that ammoniacal silver nitrate could penetrate nails and other keratin-containing material rapidly and to a considerable depth. These observations, coupled with the lack of observed reaction on dry skin and the decided fungicidal properties observed for lesions on the dry skin, made the substance appear worthy of clinical trial in cases of onychomycosis.

Direct examination of scrapings and cultures of the scrapings were carried out in all cases in which a pathologic condition of the nails was suspected to be of mycotic origin.[1] All proved fungous infections of the nails were treated. Some cases in which the diagnosis was suspected but not proved were also added to this study, because of a decided clinical resemblance to the proved cases and with the hope of benefiting the patients, although the diagnosis was not onychomycosis.

The affected area was painted once weekly with the ammoniacal silver nitrate solution and allowed to dry. Usually one nail of each patient was left untreated, as a control, but, since there have been few occasions of spontaneous cure in these infections, this procedure was only a precaution. Moreover, the treated nail turns intensely black, and progress can readily be followed. The new nail grows in free of infection, and the line of demarcation between the treated nail and the new growth is clearly drawn by the staining of the nail. Treatment was carried on for various periods of time, as indicated in the table. A patient was judged cured by the appearance of the nails and by failure to demonstrate fungous elements in direct examination of scrapings and by negative cultures.

Sections of infected and sound and treated and untreated nails were removed for histologic observation and comparison. One thorough application of ammoniacal silver nitrate to the surface of the nails was sufficient to result in the complete penetration of the nail by this substance; the nail in contact wtih the nail bed was blackened. Lateral diffusion of the ammoniacal silver nitrate, applied as 1 drop to the surface of the nail, was small in comparison with the depth of penetration into the nail. For treatment, the ammoniacal silver nitrate must be spread over the nail as a film. The penetration of ammoniacal silver nitrate into nails was studied histologically and also by roentgenogram. Examples are shown in figures 1 and 2, and these will be discussed later in this paper.

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1. Miss Louise A. Kelly, Technician in Dermatology, Tufts Medical School, gave assistance in this aspect of the work.

The ammoniacal silver nitrate used in this study[2] was a liquid of high purity, having the following physical characteristics:

Density	1.510	to	1.520	per cent
Silver content	29.50	to	30.50	per cent
Ammonia content	9.35	to	9.60	per cent
Ratio of silver to ammonia	3.10	to	3.30	
Freezing point	10.0	to	20.0	C.

There was no free silver ion (Ag^+) or free ammonium hydroxide in the preparations used. All silver was present as the complex salt $Ag(NH_3)_2NO_3$, which dissociates as the complex ion $Ag(NH_3)_2^+$. The chemical was dispensed from 2 cc. amber glass ampules; a small quantity of the liquid was shaken into a small deep dish, from which it was taken up into small capillary pipets operated by means of an at-

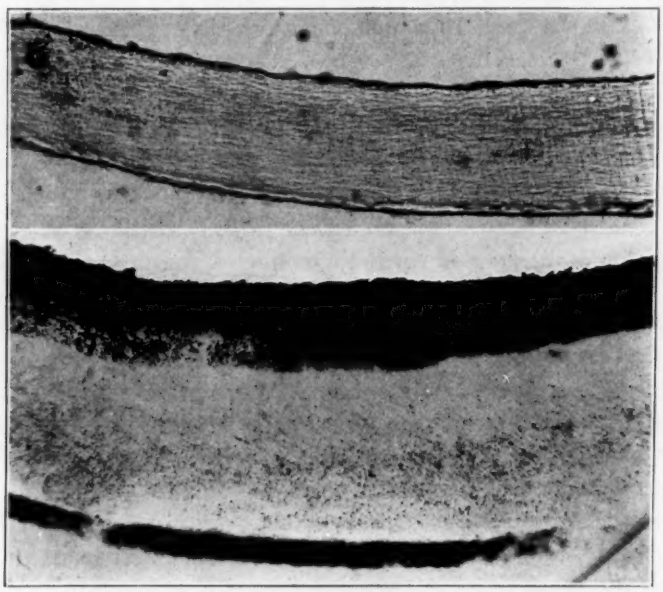

Fig. 1.—Cross sections of treated nail (lower, × 200) and untreated (upper, × 85) normal nail, showing the pattern of penetration of ammoniacal silver nitrate. The top surface of the nail was coated lightly with no. 3 solution of ammoniacal silver nitrate; the bottom surface (distal) was faintly coated to delimit the lower boundary. With full treatment the nail is completely penetrated by the ammoniacal silver nitrate. The nails were fixed in Bouin's fluid and embedded in celloidin in sections of 10 mg. (Photomicrographs were made by Mr. Frank White, Biological Laboratories, Harvard University.)

tached sealed rubber tube. With the aid of the capillary it was easy to distribute the liquid where desired. In some of our work the ammoniacal silver nitrate was reduced to metallic silver *in situ* by use of eugenol after time had elapsed for penetration of the ammoniacal silver nitrate into the nail; this procedure resulted in the deposition of metallic silver within the nail.

2. Mr. P. N. Condit of the P. N. Condit Co., Back Bay Station, Boston, supplied the ammoniacal silver nitrate used in this study.

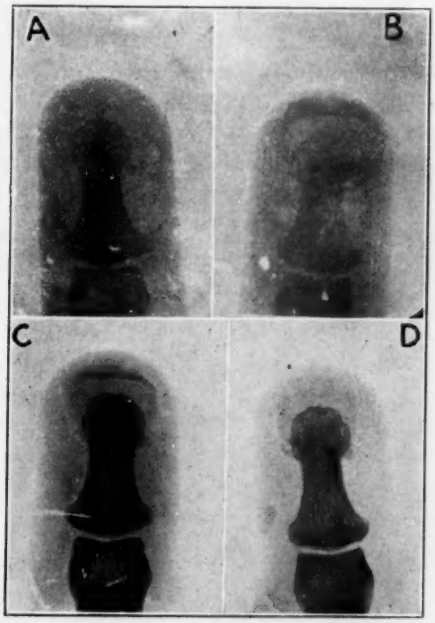

Fig. 2.—Roentgenograms of a finger with a normal nail. The nail in *A* (control) is not visible. *B, C* and *D* show a nail painted with ammoniacal silver nitrate at intervals of twenty-four hours, two hours and one hour respectively after the first application. The outline of the nail becomes increasingly visible.

Effect of Treatment of Fungous Infections of the Nails with Ammoniacal Silver Nitrate

Case No.	Diagnosis	Organism	Duration of Infection	Cured	Definite Improvement	No. of Treatments
1	Onychomycosis	C. albicans	2 yr.	X		4
2	Omychomycosis	C. albicans	5 yr.		X	5
3	Onychomycosis	C. albicans	3 yr.		X	2
4	Onychomycosis	C. albicans	1 yr.		X	2
5	Onychomycosis	C. albicans	6 mo.		X	4
6	Onychomycosis	C. albicans	3 yr.	X		3
7	Tinea ungium	T. rubrum	15 yr.	X		8
8	Tinea ungium	T. rubrum	2 yr.		X	1
9	Tinea ungium	T. rubrum	4 yr.	X		10
10	Tinea ungium	T. rubrum	3 yr.	X		3
11	Tinea glabrosa	T. rubrum	6 mo.	X		5
12	Moniliasis	C. albicans	2 yr.		X	5
13	Tinea circinata	E. floccosum	4 mo.	X		1
14	Onychomycosis	C. albicans	3 yr.	X		8
15	Tinea ungium	T. rubrum	1 yr.	X		5
16	Tinea ungium	T. rubrum	9 mo.		X	3

Results of our study are summarized in the table. Of the 16 patients treated, all responded favorably; 9 have been classed as cured, as evidenced by the growth of normal-appearing nail tissue proximal to the treated area and the normal mycologic observations, as mentioned previously; 7 were classed as definitely improved and may be transferred to the "cured" column with a few more treatments. The disease in case 7, which had existed for fifteen years, healed following eight treatments. In other cases, in which the duration varied from four months to three years, there was also cure. Considerable improvement was noted in the other patients; they were still receiving treatment

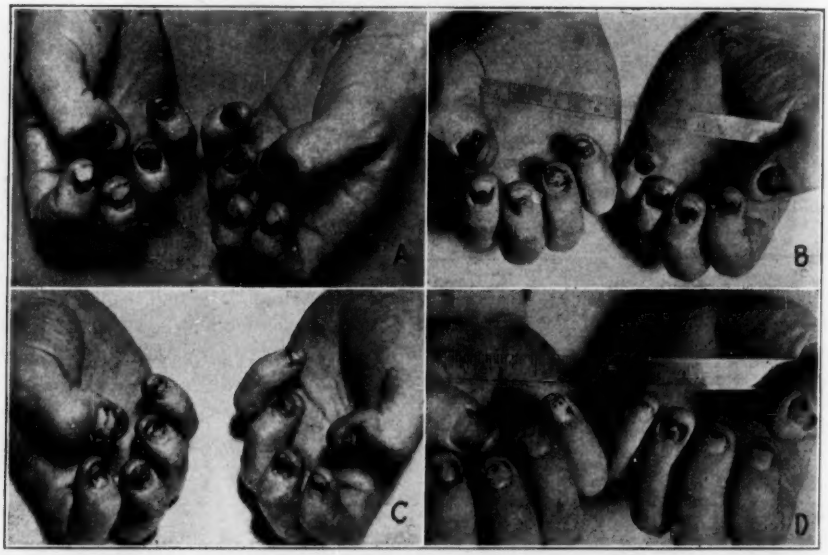

Fig. 3.—Progress in the case in which there was Trichophyton rubrum infection of the nails and palms, of two years' duration. Treatment with ammoniacal silver nitrate commenced Jan. 10, 1947. *A*, appearance on January 21. *B*, appearance on February 14. *C*, appearance on March 6. *D*, appearance on March 29. By following the grooves in the nails, one can note the rate of nail growth and improvement. The palms were entirely clear (*C*) by March 6. The improvement in the lesion at the base of the left palm can be seen. The infection was entirely cleared up, but the nail on the left thumb, which had been surgically evulsed prior to the beginning of this treatment, is still somewhat abnormal (but free of infection).

at the date of writing. In case 7 the disease had persisted after three separate surgical removals of the infected nails. The progress in 1 case is shown in figure 3.

No unfavorable reaction was noted in any case. Some patients reported that there was some pain locally, about the nail, for up to an hour following the treatment, but in no case was this severe enough to result in any objective observations or to discourage the patient in further treatment.

COMMENT

Keratin, of which the nails are composed, is a protein that is insoluble in water, organic solvents, dilute acids and dilute alkalis and, in turn, is not penetrated by substances in aqueous solution or other solvents. The decomposition of keratin by the dermatophytes may be accomplished by a preliminary reduction of disulfide links followed by enzymatic action (Nickerson and Williams[3]). The property of ammoniacal silver nitrate of penetrating nails is unusual but definite, as the accompanying roentgenograms[4] and photographs of histologic sections of treated and untreated nails show. Work is continuing to determine how ammoniacal silver nitrate effects the penetration of nail tissue. The resistance of infections of the nails to treatment in the past has had its basis in the impermeability of the keratin to dissolved materials. The fungi growing in the nails have thus not been affected by the undeniable fungicidal or fungistatic powers of the substances applied in treatment. With ammoniacal silver nitrate, which penetrates the keratin rapidly and which has an extremely high phenol coefficient, the fungi encased and embedded in the nail are rapidly killed.

SUMMARY AND CONCLUSIONS

A preliminary report of a new mode of treatment for fungous infections of the nails is presented.

The substance used was ammoniacal silver nitrate, which is an active fungicide and also possesses the property of penetrating keratin.

Penetration by the ammoniacal silver nitrate was demonstrated by roentgenograms of the nails and by histologic study.

Patients with fungous infections, proved by scraping and by culture, were treated with weekly applications of an ammoniacal silver nitrate solution.

No unfavorable reactions were noted.

Sixteen cases are reported. Nine patients have been cured. "Cure" is demonstrated by the growth of normal-appearing nail tissue and normal mycologic observations. The remaining 7 were definitely improved and, as of the date of writing, continued to receive treatment.

Because of the highly unusual property of penetrating nail tissue, reaching the nail bed and, thus, exerting direct fungicidal action on the hitherto unapproachable fungi, ammoniacal silver nitrate appears to offer a better prospect for cure of these extremely stubborn conditions than any previous method of treatment. Further study is in progress.

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3. Nickerson, W. J., and Williams, J. W.: Metabolic Products of Pathogenic Fungi, in Nickerson, W. J.: Biology of Pathogenic Fungi, Waltham, Mass., Chronica Botanica Co., 1947.

4. Dr. Charles F. Collela, Mansfield, Mass., took the roentgenograms shown in the illustrations.

PENICILLIN THERAPY OF YAWS AND SEROLOGIC RESULTS

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SOON after Mahoney, Arnold and Harris[1] demonstrated the efficacy of penicillin therapy in early syphilis, reports appeared in the literature attesting to a similar beneficial role in the treatment of yaws. The earlier publications[2] (table 1) indicated rapid clinical

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1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Therapy in Syphilis, Am. J. Pub. Health **33**:1387, 1943.

2. (*a*) Whitehill, R. C., and Austrian, R.: Treatment of Primary and Secondary Yaws with Penicillin, Bull. Johns Hopkins Hosp. **75**:232, 1944; Treatment of Yaws with Penicillin, Bull. U. S. Army M. Dept., 1945, no. 86, p. 84. (*b*) Lofgren, R.: Yaws Treated with Penicillin: Report of Case, U. S. Nav. M. Bull. **43**:1025, 1944. (*c*) da Cunha, A. M.: Area Leão; Nery Guimarães, F. N., and Cardoso, H.: Penicillin in the Treatment of Yaws Spirochetosis, Foreign Letters (Brazil), J.A.M.A. **126**:1163 (Dec. 30) 1944. (*d*) da Cunha, A. M., and Area Leão, A.: Penicillin in the Treatment of Frambesia, Foreign Letters (Brazil), ibid. **128**:1120 (Aug. 11) 1945. (*e*) Findlay, G. M.; Hill, K. R., and Macpherson, A.: Penicillin in Yaws and Tropical Ulcer, Correspondence, Nature, London **23**:795, 1944. (*f*) Tompsett, R. R., and Kauer, G. L.: Penicillin Treatment of Early Yaws, Am. J. Trop. Med. **25**:275, 1945. (*g*) Dwinelle, J. H.; Rein, C. R.; Sternberg, T. H., and Sheldon, A. J.: Preliminary Report on the Evaluation of Penicillin in the Treatment of Yaws, ibid. **26**:311, 1946. (*h*) Nery Guimarães, F. B.: Treatment of Tertiary Lesion with Penicillin: Gummatous Ulcerations, Periostitis, Osteitis, Areas of Osseous Rarefaction and Gangosa (Rhinopharyngitis Mutilans); Preliminary Report, Brasil-med. **59**:89, 1945. (*i*) Stubenford, W. D.: Yaws: Treatment with Penicillin, South. M. J. **39**:608, 1946. (*j*) Hill, K. R.; Findlay, G. M., and Macpherson, A.: Treatment of Yaws with Penicillin, Lancet **2**:522, 1946.

cure with relatively small doses of penicillin, but only a few patients attained seronegativity with the tests employed. In a preliminary report[2g] published by us, the short term results of treatment of 500 patients with early yaws infections in Haiti were discussed. Penicillin was observed to hold definite promise as a therapeutic agent, but the serologic response at the end of three and six month intervals was

TABLE 1.—*Results Reported in the Literature*

Authors	Patients Treated	Dosage Schedule	Clinical Cures	Serologic Results
Whitehill and Austrian (1944-1945)[2a]	41	15,000 every 4 hr. for 5-6 days Total dose, 500,000 O.U.	1 week	None seronegative at end of 20 weeks
Lofgren (1944)[2b]	1	1,500,000 O.U. in 12 days	13 days	Kahn reaction negative after 5 weeks
da Cunha, Area Leao, Nery Guimaraes and Cardosa[2c]	7	9,600-52,000 O.U.	14 days	Wassermann reaction negative in all cases in 60 days
da Cunha and Area Leao (1945)[2d]	5	9,600-52,000 O.U.	14 days	Wassermann reaction negative in all cases in 60 days
Findlay, Hill and Macpherson (1944)[2e]	24	50,000 to 100,000 O.U. in 12-24 hr.	6-7 days	Reaction became negative (Kahn) in 7 days in 2 cases of primary disease
Tompsett and Kauer (1945)[2f]	5	250,000 to 400,000 O.U. in 2-4 days	1-3 days	Not done
Dwinelle, Rein, Sternberg and Sheldon (1946)[2g]	500	600,000 to 1,200,000 O.U. in 1-4 days	Within 1 mo.	10% became seronegative at the end of 6 mo. with the Kahn test
Nery Guimaraes (1945)[2h]	6	200 O.U. every 4 hr. to 9,600 O.U. daily. Period of treatment 20 days-7 mo., 18 days. Total dose 48,000-558,800 O.U.	2 to 7 mo.; bone lesions not completely cured	Only 1 case reported; Wassermann reaction negative after 2 mo.
Stubenford (1946)[2i]	1	200 O.U. every 3 hr. Total dose, 1,500,000 O.U.	15 days	No essential change in Kahn reaction after 5 mo.
Hill, Findlay and Macpherson (1946)[2j]	128	100,000 daily; total dose, at least 1,000,000 O.U.	Primary, 9 days; secondary, 8½ days; tertiary, up to 16½ days with 2 failures	Seronegativity obtained in 1 case at end of 3 mo.; in 5 at end of 6 mo.; in 13 at end of 9 mo.; in 1 at end of 12 mo

surprisingly disappointing. The present report deals in detail with evaluation of the serologic results obtained in the entire group treated at the end of twelve months' observations.

METHOD

Five hundred patients with primary and secondary yaws were selected for this study and divided into three groups.

Classification.—Group A: Two hundred patients were hospitalized and given 1,200,000 Oxford units of sodium penicillin in aqueous solution over a period of four days (thirty intramuscular injections of 40,000 Oxford units every three hours, day and night). All patients, regardless of age, received the same total dose.

Group B: One hundred and fifty-one patients were treated on a two day ambulatory schedule, with amorphous calcium penicillin in peanut oil and wax, as devised by Romansky[3] (300,000 Oxford units per cubic centimeter). The dose was reduced for children according to age and weight (table 2). Children 6 to 12 years of age received 600,000 Oxford units; those 13 to 16 years of age received 900,000 Oxford units, and those 17 years and over were given 1,200,000 Oxford units. The penicillin was given intramuscularly in divided doses twenty-four hours apart.

Group C: One hundred and forty-nine patients were treated on a one day ambulatory schedule, with the same amorphous calcium penicillin in peanut oil and wax. The same modification of dosage according to age was employed as in Group B, but the doses were administered ten to twelve hours apart.

Specimens.—A blood specimen for serologic examination was collected from each patient immediately prior to treatment. The blood was permitted to clot and was sent to the Central Laboratory, where the specimen was centrifuged and

TABLE 2.—*Dosage by Groups*

Age Groups	5 Yr. and Under	6-12 Yr.	13-16 Yr.	17 Yr. and Over	Total No. of Patients
Group A Total dosage penicillin in 4 days	13 1,200,000 O.U.	60 1,200,000 O.U.	41 1,200,000 O.U.	86 1,200,000 O.U.	200
Group B Total dosage penicillin in 2 days	0 O.U.	74 600,000 O.U.	27 900,000 O.U.	50 1,200,000 O.U.	151
Group C Total dosage penicillin in 1 day	0 O.U.	56 600,000 O.U	35 900,000 O.U.	58 1,200,000 O.U.	149
Total no. patients	13	190	103	194	500

the supernatant clear serum removed. The serum was placed in vials containing sufficient powdered merthiolate[4] (sodium ethylmercuri thiosalicylate from Eli Lilly and Company) so that the final concentration of the preservation was 1 mg. per cubic centimeter of serum.

The merthiolated serum specimens were shipped by air to the Division of Serology, Army Medical School, Army Medical Center, Washington, D. C. Less than 1 per cent of the specimens arrived there in a condition unsatisfactory for

3. Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin, Science **100**:196, 1944.

4. The efficacy of merthiolate as a bacteriostatic and bacteriocidal agent for the preservation of serums, antigens, vaccines, plasma and other biologic products has been established for many years. In a previous study it was shown that specimens preserved with 1 mg. of merthiolate per cubic centimeter of serum were satisfactory for serologic testing. (Rein, C. R., and Bossak, H. N.: Merthiolate [Sodium Ethyl Mercuri Thiosalicylate] as a Preservative in Sera for the Serodiagnosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:342, 1946.) This preservative did not produce nonspecific reactions in negative serums or any appreciable change in serologic titer in positive serums.

testing as the result of bacterial contamination. Each specimen was subjected to a "battery" of qualitative and quantitative procedures, including the Kline diagnostic test, Kline exclusion test, Mazzini and Boerner-Jones-Lukens microflocculation tests, Kahn standard macroflocculation test and Kolmer complement fixation tests. Later in the study, the Boerner-Jones-Lukens test was replaced with a new microflocculation[5] procedure[6] employing cardiolipin antigen.

Following treatment, additional blood specimens were collected at monthly intervals from the patients in group A and at three month intervals in groups B and C. Each of these serum specimens was also preserved with merthiolate and sent to the Army Medical School for testing.

CLINICAL RESULTS

The results in respect to clinical improvement have appeared in our previous report.[2g] Only a summary will be given here.

Clinical improvement was rapid and remarkable; joint pains disappeared in from twenty-four to forty-eight hours; plantar and palmar "crab" lesions became painless in from forty-eight to seventy-two hours; primary and secondary lesions were in the desiccation stage in four days, at which time the crusts could be easily removed, revealing a dry and well healed underlying skin. Complete healing of all lesions was observed in most instances on the first reexamination, one or three months following completion of treatment. A few ulcerated primary lesions still presented a purulent discharge. No toxic reactions from the penicillin therapy were observed, although approximately one half of the patients in the hospitalized group showed a temporary rise in temperature (100 to 104 F.) shortly after institution of treatment. In 1 patient in group B, pain, heat, redness and swelling developed at the site of injection of penicillin in peanut oil and wax. Dark field examinations gave negative results in from eight to ten hours. Stained sections made from biopsy material showed numerous spirochetes up to twelve hours, only an occasional isolated spirochete from twelve to twenty-two hours and none thereafter.

SEROLOGIC RESULTS

In all the 500 patients examined, one or more of the tests previously described elicited seropositive reactions. These reactions were not different from those observed in primary and secondary syphilis, except that more zone reactions were observed in patients with yaws. These zone reactions occurred in strongly positive serums from patients with secondary yaws. In some instances the serums gave nega-

5. Rein, C. R., and Bossak, H. N.: Cardiolipin Antigens in the Serodiagnosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:40, 1946.

6. Rein, C. R., and Bossak, H. N.: Cardiolipin Antigens in the Serodiagnosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:40, 1946.

tive reactions to the qualitative tests and gave positive reactions only to the quantitative procedures. These positive serologic reactions which occur in certain treponemal (syphiloid) diseases should not be considered false positive reactions.[7] Diseases such as yaws, bejel and pinta are caused by organisms closely related to Treponema pallidum and give rise to positive serologic reactions identical with those obtained in syphilis. During the past few years several laboratory procedures have been designed to differentiate between true and false positive reactions. With the Kahn verification tests,[8] the Rein- Pillimer inhibition test[9] and the Neurath euglobulin inhibition procedure,[10] it has not been possible to differentiate between the positive reactions obtained in patients with yaws or pinta and those observed in patients with syphilis.

In our preliminary report[2g] it was noted that although the majority of patients in group A showed a definite progressive reduction in serologic titer during the first six months after treatment, only 10 per cent attained seronegativity at the end of this period. In general, this was true also of patients in groups B and C three months after treatment with penicillin in peanut oil and wax. In order to evaluate the serologic results obtained in these cases in a twelve month follow-up period, the following arbitrary criteria and definitions were decided on:

Serologic Cure.—Serologic cure denoted seronegativity attained and maintained following treatment.

Serologic Improvement.—Serologic improvement constituted a reduction in serologic titer, indicating a satisfactory serologic response, but seronegativity not attained.

Serologic Fastness.—Serologic fastness indicated failure to show a reduction in serologic titer below the pretreatment level.

Serologic Relapse.—Serologic relapse constituted an initial reduction in serologic titer followed by a sudden and progressive increase in titer, indicating an unsatisfactory response to penicillin therapy, or serologic failure of this treatment.

In this study, the results reported are limited to those obtained with the Kahn standard and quantitative tests. This is done in order to facilitate comparison of our results with those of other investiga-

7. Rein, C. R., and Elsbery, E. S.: Studies on the Incidence and Nature of False Positive Serologic Reactions for Syphilis, Am. J. Clin. Path. **14**:461, 1944.

8. Chargin L., and Rein, C. R.: The Kahn Verification Test: An Appraisal of the Test Based on Clinical and Serologic Evidence, Arch. Dermat. & Syph. **44**:1031 (Dec.) 1941.

9. Rein, C. R., and Pillimer, L.: A New Inhibition Procedure to Differentiate the Syphilitic from the Nonsyphilitic Serologic Reaction, to be published.

10. Neurath, H.: Personal communication to the authors.

tors, since the majority of publications pertaining to treatment of yaws are based on serologic results obtained with Kahn tests. Furthermore, in the majority of reports dealing with penicillin therapy in syphilis, the reaction to the Kahn test is also employed as a serologic measuring rod. It should be pointed out, however, that the evaluation of our results would be somewhat different if it had been based on reactions to more sensitive tests. The serologic pattern and the degree of serologic improvement evidenced by the reactions to the various tests were similar.

The serologic results following treatment are given in table 3. It will be noted that in group A, 25.1 per cent attained seronegativity and 68.7 per cent showed serologic improvement, giving a total of 93.8 per cent who could be classified as showing satisfactory progress. In group B, only 11.0 per cent attained seronegativity while 81.9 per cent showed serologic improvement, giving a total of 92.9 per cent who could be classified as showing satisfactory progress. In group C, only 6.4 per cent attained seronegativity while 86.4 per cent showed serologic improvement, a total of 92.8 per cent who could be classified as showing satisfactory progress.

TABLE 3.—*Serologic Results Following Treatment*

Groups	Serologic Cure	Serologic Improvement	Serologic Relapse	Serologic Fastness
A	25.1%	68.7%	4.6%	1.5%
B	11.0%	81.9%	5.5%	1.5%
C	6.4%	86.4%	4.8%	2.4%

Groups	Serologic Cure and Improvement
A	93.8%
B	92.9%
C	92.8%

COMMENT

As stated before, the clinical response of lesions of primary and secondary yaws to penicillin therapy was uniformly and invariably excellent. The rapid and complete healing of generalized large lesions of frambesia was dramatic. The serologic response, however, was different. In the 477 patients the course of whose disease was followed up by serologic studies, only 71 (15.8 per cent) attained seronegativity. Had a less sensitive test been employed, a higher incidence of serologic cures might have been obtained. It is possible that some of the earlier

investigators, who reported a higher percentage of cures in a short period of time, used serologic procedures of low sensitivity levels.

As in syphilis, there are a number of factors which influence the length of time required to attain seronegativity.[11]

(*a*) *Stage of the Disease.*—The older the disease, the longer it takes for the body cells to stop forming reagin. As a rule, patients with secondary yaws require more time to acquire seronegativity than do patients with seropositive primary lesions.

(*b*) *Serologic Response of Individual Patients.*—In some patients with yaws there develop more antibodies or reagin than in others in response to the same type of stimulus. Those in whom more antibodies or reagin develops usually require more time to attain seronegativity.

(*c*) *Serologic Titer.*—As a rule, patients with high serologic titers at the beginning of treatment require more time to attain seronegativity than do those with relatively low titers.

(*d*) *Sensitivity of the Serologic Procedure.*—The more sensitive the serologic test, the longer it takes to attain seronegativity. When a serologic "battery" consisting of tests of varying sensitivities is employed, as in this study, negative reactions may be obtained with the less sensitive tests long before negative reactions occur with the more sensitive tests.

(*e*) *Type of Tests.*—Certain types of tests may continue to elicit positive results long after other tests elicit negative reactions, even though they are in the same relative range of sensitivity.

(*f*) *Treatment Schedule.*—The type of penicillin used, the amount and the time required to administer it may also affect the length of time needed to attain seronegativity.

Evalation of Influencing Factors.—It must be pointed out, however, that these factors are subject to many variations and no set rules can be laid down at this time by which the length of time required to attain seronegativity can be determined or anticipated.

The serologic response in yaws is certainly much slower and less satisfactory than that observed in the treatment of early syphilis with a similar amount of penicillin.[12] One of the reasons for this difference may be that in syphilis, treatment is usually started within a few weeks after the development of cutaneous manifestations, whereas the majority of the patients in this study had had yaws for many months.

It is also possible that many more of the patients with yaws in this study may attain seronegativity during the second or third year fol-

12. Sternberg, T. H., and Leifer, W.: Treatment of Early Syphilis with Penicillin, J.A.M.A. **133**:1 (Jan. 4) 1947.

lowing treatment. Some patients[11a] with secondary syphilis, who were treated with penicillin and for whom results were still seropositive at the end of twelve months, attained seronegativity during the second year without additional treatment.

From this study it seems that the amount of penicillin administered did not appreciably affect the incidence of serologic cures. In group A, all patients received the same total dosage (1,200,000 Oxford units). Although in the majority of the cases in children in this group the dosage in proportion to body weight was five times as great as that given to the adults, the serologic response differed in no respect from that of the adults. On the other hand, the duration of treatment may have some effect. It will be noted that the patients in group A, who received their treatment during a period of four days, showed a rate of serologic cure of 25.1 per cent; those in group B, who received their treatment in two days, attained a serologic cure rate of 11.0 per cent, and those in group C, who received the same total dosage in one day, showed a rate of cure of only 6.4 per cent. Thus, there was a definite reduction in the percentage of serologic cures as the duration of treatment was shortened, even though the total dosage was constant.

In this study it was not possible to determine whether serologic relapse was associated with clinical relapse or with reinfection. With the introduction of penicillin therapy for early yaws, some patients are attaining clinical and serologic cures earlier than heretofore. Since these "cured" patients are constantly exposed to persons with active lesions of yaws, reinfections are probably of frequent occurrence. The criteria for indisputable reinfection are rather rigid, and, unfortunately, these patients are not observed at sufficiently frequent intervals to satisfy all the requirement. Therefore, it is often difficult, and sometimes impossible, to determine whether a new infection has been acquired or a relapse has occurred in the old infection. At the Army Medical School we have had some experience with follow-up serologic studies of patients with early syphilis treated with penicillin. A "battery" of serologic tests was made on serums of patients at daily, weekly and monthly intervals. From our observation we feel that it may be possible in some instances to distinguish between relapse and reinfection by carefully conducted quantitative serologic studies made at frequent intervals. Following penicillin therapy in patients with early syphilis, there is usually a progressive reduction in serologic titer. In cases of reinfection the patients usually attain and maintain

11. (*a*) Romansky, M. J., and Rein, C. R.: Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, J.A.M.A. **132**:847 (Dec. 7) 1946. (*b*) Rein, C. R.: Recent Advances in the Serodiagnosis of Syphilis, J. Michigan M. Soc. **46**:541 (May) 1947.

complete seronegativity followed by the development of a dark field positive seronegative lesion at a new site. Shortly afterward, seropositive reactions develop with rapidly increasing titers. There is even some evidence to indicate that in some patients with a residual positive serologic reaction from a previous infection, a new primary lesion may develop at another site (reinfection or superinfection). In cases in which treatment failed or in which there was relapse there was first noted a sudden increase in serologic titer followed, in about one month in the majority of instances, by clinical evidence of a mucocutaneous relapse.

The same serologic differentiation between relapse and reinfection may be possible in yaws. If patients treated with penicillin could be subjected to serologic examinations at weekly or monthly intervals, it might be possible to predict, on the evidence of a progressive increase in serologic titer, a clinical relapse about one month before the appearance of clinical evidence.

It may be that some of the cases classified under "clinical relapse" should actually be classified under "reinfection." In evaluating a treatment schedule, it is unfair to consider treatment in these cases as having failed, since every classification of reinfection as relapse or failure causes a reduction of 2 per cent in the final rate of cure.

In this study, in 1 patient there was reversion to seronegativity prior to the appearance of a supposedly new primary lesion. As for the other cases in which new lesions developed, in approximately half an increase in serologic titer developed one or two months before the appearance of the new lesions (relapse?), while in the rest, an increase in serologic titer was noted simultaneously with or soon after the appearance of the new lesion (reinfection?).

It was also noted that some of the patients in this study had been treated previously with oxophenarsine hydrochloride ("mapharsen") and/or bismuth compound and had subsequently suffered a relapse or had become reinfected. Their clinical and serologic response to treatment with penicillin was similar to that of previously untreated patients.

CONCLUSIONS

Based on clinical response, pencillin is probably the drug of choice in the present day treatment of yaws. Penicillin in a peanut oil and wax vehicle (Romansky formula) is of value in countries such as Haiti, where the majority of patients must be treated in the shortest period of time and on an ambulatory basis in rural clinics.

The clinical results obtained with penicillin were consistently and invariably good. They were definitely better and were obtained more

rapidly with penicillin than with the previously employed arsenic and bismuth compounds. Furthermore, a maximum amount of penicillin could be administered in a minimum period of time without fear of serious untoward reactions.

Although the majority of patients (approximately 93 per cent) showed satisfactory serologic progress, only 15.8 per cent had attained seronegativity at the end of a twelve month follow-up period.

58 Fifth Avenue.

ABSTRACT OF DISCUSSION

Dr. Udo J. Wile, Ann Arbor, Mich.: Dr. Rein is one of the few expert serologists, if not the only one, who is at the same time a practicing clinician in our specialty. If more so-called serologic experts were clinically trained, less confusion would exist between laboratory procedures as they apply to clinical medicine.

The outstanding point of interest in Dr. Rein's presentation is the ease with which the clinical manifestations of yaws disappear with penicillin therapy, by injection with a water-soluble base and by injections with wax and peanut oil. In striking contrast to this, however, are the rather disappointing serologic responses accompanying clinical recovery.

Only 15.8 per cent of patients with primary and secondary yaws in a series of 500 had achieved seronegativity after one year's observation. Contrasting this with the 70 per cent of seronegative results in primary and secondary syphilis with the same dose in the same time interval, these figures are decidely disappointing. The discrepancy in the serologic outcome is not readily explainable.

Several possible hypotheses suggest themselves: first, that yaws is a more resistant disease or, better expressed, that Trepohema pertenue is more resistant to penicillin than is the syphilis organism; second, that the lower physical state of the natives of Haiti is a factor; third, that the immune mechanism of yaws is a different phenomenon than that occurring in syphilis and, finally, from a historical standpoint, yaws was more or less an epidemic problem in Haiti at least three hundred years before syphilis became a problem in the western part of the world.

Of all of these possibilities, those pertaining to the antiquity of yaws and, in consequence, to the immunologic processes of the disease would appear to me to be the more likely reasons for the differnce in the serologic response.

Studies of this kind, if pursued, may, it is to be hoped, shed some light on the relation between these two spirochetal diseases. Yaws and bejel have considerably more in common in their nature and the condition under which they occur than either or both have with syphilis. Mutation in various infectious diseases is known to occur under varying conditions of life.

Notwithstanding the apparent great difference in serologic response between syphilis and yaws, the suggestion that both yaws and bejel are mutations of syphilis, nonsexually contracted, in some instances perhaps vector borne, is still an attractive hypothesis.

Dr. Everett C. Fox, Dallas, Texas: Most of the Army medical officers in the Pacific area had opportunity to observe many cases of yaws. They set up clinics for the natives on most of the islands in military areas.

It was interesting to those who had not seen yaws to see practically all of the children and youngsters with verrucae or cauliflower excrescence and primary

lesions on the feet, and all of the youngsters under 10 or 12 years of age either had these lesions or had had them previously.

Prior to the time when the Army medical officers appeared, a number of the natives had been treated with bismuth salicylate over a period of months, but progress was slow. By the time two or three doses of oxophenarsine hydrochloride ("mapharsen") had been given the children could begin to run and play again. The older patients showed all the osseous changes seen when the disease had started many years prior to the time of examination.

Early in 1944, my colleagues and I treated one of the native boys, who had eleven osseous gummatous lesions, with penicillin, and the gummatous lesions healed rapidly. It was interesting to notice the small number of treatments that gave good results.

I was interested in hearing Dr. Rein's report on the serologic and clinical results in the treatment of yaws with penicillin.

DR. ARTHUR G. SCHOCH, Dallas, Texas: I was so favorably impressed with Dr. Rein's paper that I read it carefully three times. I think that he takes too pessimistic a view concerning the dosage schedules employed, which seem to be short in duration and a bit inadequate as to total dosage.

I was impressed by the figures for infectious relapse given for his patients. They were in the neighborhood of 5 per cent for each one of these groups. If one measures the results of treatment on the basis of the number of patients who at some later date exhibit clinical failure, rather than include with that group those in whom there is lack of serologic response, these figures take on an entirely different aspect. My experience with penicillin schedules in treatment of syphilis yielded an over-all incidence of infectious failure of 12 per cent in a group of over 1,100 patients.

That is twice the number observed by Dr. Rein, so that I think that he is too pessimistic.

DR. CHARLES R. REIN: Although yaws and syphilis are rather similar in many respects, it should be emphasized that they do differ in the serologic response to treatment. The serologic response in yaws is certainly much slower and less satisfactory than that observed in the treatment of early syphilis with a similar amount of penicillin. There are a number of theories to explain this failure of serologic response. One of the factors may be that the majority of patients in this series had yaws for many months or years, whereas, in early syphilis, treatment is usually started within a few weeks after the development of the cutaneous manifestations. There is sufficient evidence that the older the infection, the longer it takes for the attainment of seronegativity.

In order to improve the incidence of serologic cures another study has been started in Haiti, utilizing only crystalline penicillin G in peanut oil and wax, in schedules of 1,200,000 and 2,400,000 units administered on an ambulatory basis during a period of two to four days. In a country like Haiti treatment schedules lasting more than two days are rather impractical and sometimes impossible.

We also noted that the location, climate and atmospheric conditions produced various changes in the clinical manifestations and course of the disease.

TOCOPHEROLS (VITAMIN E)

Treatment of Lupus Erythematosus; Preliminary Report

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WITH THE knowledge that the administration of tocopherols (vitamin E) had, in sufficient dosage, demonstrated a profound ability to regenerate collagenous tissue in a case of noduloulcerative granuloma with lipoidal deposits, indistinguishable from necrobiosis lipoidica diabeticorum,[1] it was logical that certain other entities which have been grouped by Klemperer and his co-workers[2] as diseases affecting primarily collagenous ground substance, irrespective of causation, should be investigated and treated in similar manner.

Thus, a series of cases of lupus erythematosus were studied with a view to determining the value of mixed tocopherol therapy in this disease. Any investigative observations as to foci of infection, or other aspects not exactly pertinent to this study, are omitted.

REPORT OF CASES

CASE 1.—Mrs. C. R. A., aged 24, presented raised somewhat thickened patchy lesions of lupus erythematosus about the eyes, cheeks and sides of the neck, of about three years' duration. This had followed scarlet fever at the age of 17. Previous injection therapy (with bismuth compound) had not been of value. She was first given a daily dosage of 150 mg. of mixed tocopherols by mouth (vitamin E, "natopherol") in March 1947. Fading of the lesions becoming evident in two weeks, she was given, in addition, intramuscular injections of 250 mg. of mixed tocopherols ("natopherol") twice weekly. The improvement was more rapid, and

From the Dermatological and Pathological Departments of the Montreal General Hospital.

Abbott Laboratories supplied the "natopherol" (contains alpha, beta, gamma and delta tocopherols) used in these studies.

Mr. Frank Zahalan gave technical help and advice in this study.

1. Burgess, J. F., and Pritchard, J. E.: Noduloulcerative Granuloma of the Legs: Treatment with Tocopherols, Arch. Dermat. & Syph. **57**:605-614 (April) 1948.

2. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569-631 (Oct.) 1941.

1,750 mg. of mixed tocopherols was given intramuscularly over a period of three weeks, when all traces of the eruption disappeared.

At the end of this time, her skin, which had been without visual evidence of comedos or dilated follicles, showed many comedos over the temples.[3] These disappeared at a later date. She was given a minimum dose of 50 mg. of mixed tocopherols daily, which treatment she discontinued of her own accord in August. In five weeks, there was a mild recurrence in some areas about the orbit at some of the same sites previously affected. This rapidly cleared within three weeks after further intramuscular injections. As of the time of writing she was receiving a maintenance dose of 50 mg. of mixed tocopherols daily.

CASE 2.—Miss H. W., aged 21 (sister of Mrs. C. R. A. of case 1), presented erythematous plaques with slight follicular plugging on the neck and cheeks, but no obvious atrophy. The duration of the disease was about three years. There was a history of peeling of the palms and soles prior to the onset of the eruption, which was most probably due to scarlet fever, which had occurred some time after contact with her sister. The report of biopsy, one year prior to the present examination was stated to be indicative of lupus erythematosus. Previous injection therapy (unknown) had not been successful. In addition to mixed tocopherols, 150 mg. daily by mouth, she was given 2,000 mg. of mixed tocopherols intramuscularly from April 19 to May 17, 1947. At the end of this month of treatment, no trace of the eruption could be seen nor was residual atrophy apparent. She gave a history of photosensitivity, with the result that she avoided sunlight, as her eruption would flare up. At the end of four weeks of tocopherol therapy, she exposed herself freely to sunlight and observed that she had entirely lost her photosentivity. She was given a maintenance dose of 50 mg. daily, and, at the time of writing, there was no further activity of the disease

CASE 3.—Mrs. C. E. D., aged 57, had superficial patches of lupus erythematosus on the face, neck and back for twenty-five years. She had been treated by us with gold compound, bismuth compound, sulfonamide drugs, roentgen rays, nicotinic acid, solid carbon dioxide and other drugs, with little or no sustained value. For one month, June 6 to July 9, 1947, she received 2,000 mg. of mixed tocopherols intramuscularly and a daily dose of 200 mg. by mouth, with cure of the condition at the end of the period of treatment. She then tolerated sunlight all summer, and although tocopherol therapy was continued, there was a recurrence after three months. At the time of writing, the patient was again being treated.

CASE 4.—Mrs. M. E. B., aged 45, showed typical sclerosing patches of lupus erythematosus on the back, forehead and cheeks, of six years' duration. She had had treatment with metallic compounds in the past, with some improvement. She gave a history of inability to tolerate sunlight (her 18 year old daughter could not tolerate sunlight either). Treatment was begun on March 2, 1947, when she was given a daily dose of 150 mg. of mixed tocopherols by mouth, with a few intramuscular injections at long intervals. She improved, and patches were regressing well. Oral administration of 150 mg. of mixed tocopherols was continued. The patient went to California in June. Her skin was clear of the eruption one month later, and she stated that while in California (in accordance with instructions) she spent much time in the sunlight and "acquired a tan" for the first time in her life. She discontinued taking tocopherols entirely for two months;

3. Harris, P. L.; Swanson, W. J., and Hickman, K. C .D.: Covitamin Studies: VI. Effect of Tocopherol Supplementation on the Output of Vitamin A, Carotene and Fat by Dairy Cows, J. Nutrition **33**:411-427 (April) 1947.

the eruption recurred slightly in October, but cleared up rapidly with further tocopherol therapy.

CASE 5.—Mrs. E. E., aged 45, had a fixed lupus erythematosus about the eyes and cheeks for fifteen years, for which she had received treatment with metallic compounds and other medicaments: gold compound, bismuth compound, sulfonamide drugs and solid carbon dioxide. She entered the hospital in March 1947, where with large doses of mixed tocopherols given intramuscularly and orally, she responded well, but there were residual scars, the result of former treatment with solid carbon dioxide. At the end of three months of treatment clinical cure had resulted. Further observation has not been made since June.

CASE 6.—Mrs. E. B., aged 27, a Negro woman, showed multiple fixed areas of lupus erythematosus, with follicular plugging in thickened patches on the cheeks, nose and eyebrows, of one year's duration. Previous treatment with bismuth compound had not resulted in any change, and evidence of dissemination was manifested in newer patches on the cheeks. There was a suggestive history of photosensitivity in that her cheeks and eyes became irritated on exposure to sunlight. Treatment with mixed tocopherols was begun Sept. 9, 1947, with 150 mg. given by mouth and biweekly intramuscularly injections of 250 mg. Progressive improvement followed; after one month's treatment no thickening was noted, and the pigmentation had become progressively lighter in color.

Report of Biopsy.—The first specimen (fig. 1*A*) was taken from behind the angle of the right side of the jaw in June. It showed decided hyperkeratosis and keratin plugging of the follicles. The zona granulosa was 2 to 5 cells thick. The epidermis was generally thickened and the cells hypertrophied. The rete pegs were short. In the papillary zone there was decided vasodilatation with moderate lymphocytic infiltration and edema. In the remainder of the corium there was a moderate perivascular and perifollicular lymphocytic infiltration, with some edema. At one end of the section the basal layer of the epidermis was heavily pigmented with melanin. In the remainder of the section the pigment in the epidermis was scanty, but in the subjacent part of the corium there were numerous pigment-bearing cells.

Another biopsy (six week after institution of tocopherol therapy) was made on October 21. The specimen was taken from the left frontal region at the hair line and consisted of full thickness skin (fig. 1*B*). This showed only moderate hyperkeratosis, but still decided plugging of the follicles. The zona granulosa was 1 to 2 cells thick. The width of the epidermis was significantly reduced, as compared with the previous section, and the cells generally appeared somewhat smaller. The rete pegs and papillae were well developed except in a few small focal areas, where they were flattened. Telangiectasia was minimal, and there was only slight perivascular lymphocytic infiltration here and there in the papillary and subpapillary zone. The collagen and elastic tissue showed general distribution and content compatible with normal skin. Throughout this section there was obvious melanin pigmentation of the epidermis and numerous pigment-bearing cells in the corium.

CASE 7.—Mr. R. A. R., aged 32, presented scaly and erythematous lesions of lupus erythematosus, involving the forehead, cheeks and postauricular areas, of one year's duration. A biopsy, made in May 1947, confirmed the diagnosis of lupus erythematosus. From May 23 to June 13, he received six injections of mixed tocopherols (1,250 mg.) along with 100 mg. daily by mouth. Steady improvement was noted; throughout the summer he continued the oral intake of 150 mg. daily, and in September no traces remained and follicular plugging had disappeared. Mild

acne of the cheeks developed as a result of the injections (similar to that observed in other cases). A second biopsy specimen, from alongside the site of the previous one, was then taken. As of the time of this report, the patient was receiving a daily maintenance dose of 50 mg. of mixed tocopherols.

Report of the Biopsy.—A biopsy made on May 10 showed the characteristics of lupus erythematosus (fig. 2*A*). The sections consisted of full thickness of skin,

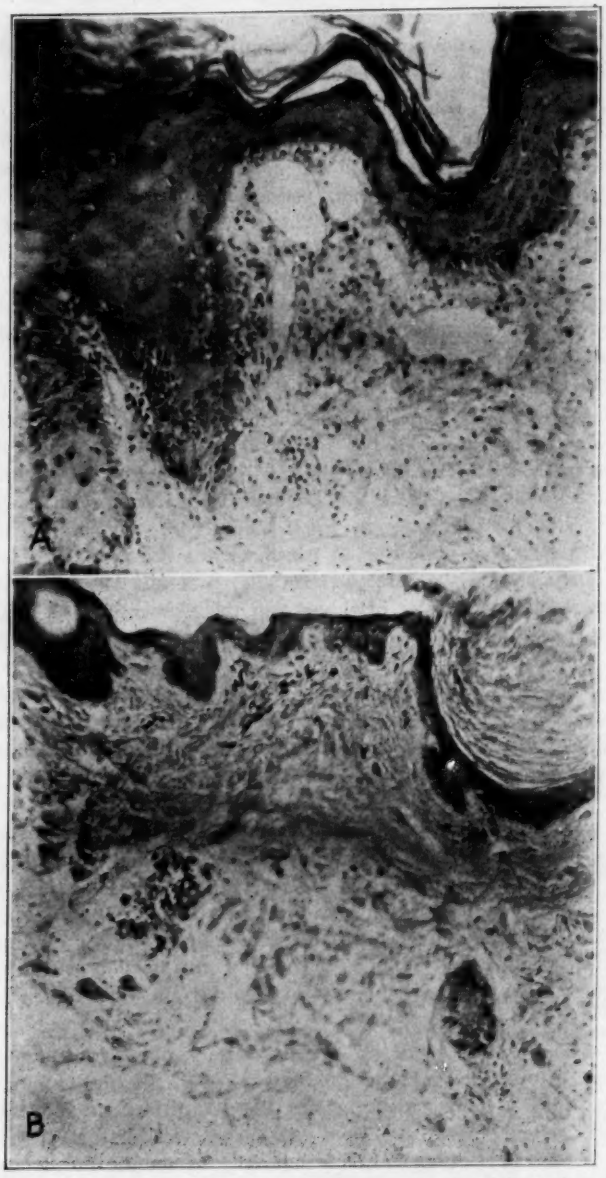

Fig. 1 (case 6).—*A*, biopsy specimen taken on June 1947, before tocopherols were administered (× 100). *B*, biopsy specimen taken October 21, after tocopherols were administered (× 100).

showing decided hyperkeratosis with follicular plugging. The zona granulosa was 3 to 5 cells thick, and there was general widening of the epidermis with hyperthrophy of the malpighian cells. The rete pegs and papillary processes were short, and in

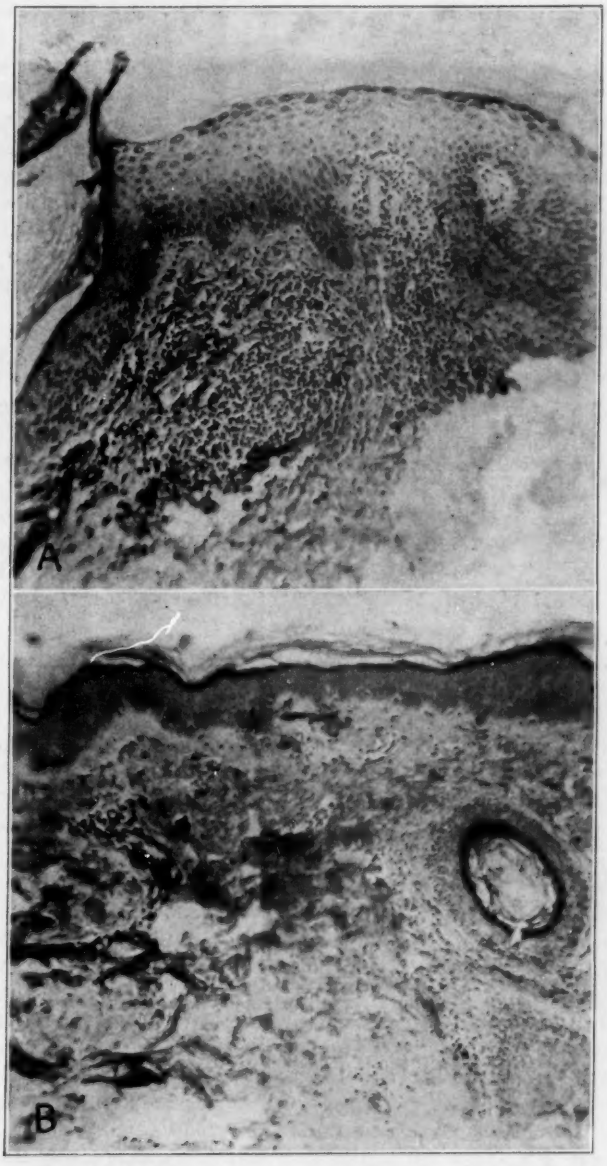

Fig. 2 (case 7).—*A*, biopsy specimen taken May 10, 1947, before treatment. *B*, biopsy specimen taken September 28, after tocopherol therapy.

most of the section the dermoepidermal junction was marked by a slightly wavy line. The basal layer was lightly infiltrated with lymphocytes. The papillary and subpapillary zones showed mild edema, with dilatation of the lymph spaces,

moderate blood vessel ectasia and moderate lymphocytic infiltration. The remainder of the corium appeared normal. The hair follicles were dilated and showed decided hyperkeratosis, the walls appearing somewhat atrophic. The elastic and collagen content and distribution were generally normal except in those areas of infiltration where the distribution was canty. Scarlet red stains showed no abnormal fatty deposits.

The second biopsy (fig. 2 *B*), made on a section taken adjacent to the site of the original one, on September 26, consisted of full thickness skin, which, compared with the original specimen in same magnification showed decided changes. There remained only moderate hyperkeratosis and follicular plugging. The granular layer was uniformly 2 to 3 cells thick. The cells here and the papillae were almost flattened; the epidermis was much narrower, and the cells were smaller. Vascular ectasia and edema were minimal, and there was only a slight lymphocytic infiltrate. The collagen was well preserved; the appendages appeared normal, and the distribution and amount of elastic tissue was comparable to that in normal skin. Scarlet red stains showed no abnormal fatty deposits.

CASE 8.—Mrs. D., aged 40, had typical atrophic and inflammatory patches on the forehead, nose, cheeks and ears, with characteristic plugging, for two years. She had had a long course of treatment with bismuth compound, with partial benefit. The report of the biopsy indicated typical lupus erythematosus. Tocopherol therapy, beginning in March, with intramuscular injections of mixed tocopherols, 250 mg. weekly, and 150 mg. taken daily by mouth, resulted in complete clinical recession of the lesions by June. The patient then disappeared from observation, but reported again in October with slight erythema in a lesion on the forehead; further tocopherol therapy resulted in recession of the lesion. As of the time of writing, she was receiving a daily maintenance dose of 50 mg. of mixed tocopherols.

CASE 9.—Mrs. L. H., aged 29, was first seen May 20, 1947, presenting ringed areas of superficial lupus erythematosus, involving each cheek and the nose with dilated follicles and some plugging, of nine months' duration. She was not photosensitive. Treatment, consisting of intramuscular injections of 250 mg. of mixed tocopherols twice weekly, caused complete disappearance of the lesions by June 13, a total of 1,500 mg. being given in three weeks. She was then told to take a daily dose of 50 mg. of mixed tocopherols orally. Further observation was not made in this case.

CASE 10.—Mr. P. F., aged 60, presented numerous thickened patches of lupus erythematosus, involving the face, ears, neck, arms and hands, of ten years' duration. There was no pliability in these areas. He had had many injections of bismuth compound, gold compound and other medicaments in the past, without benefit. While he was in the hospital for a period of two months, July and August 1947, he received 750 mg. of mixed tocopherols in weekly injections, along with 150 mg. daily, by mouth. Progressive improvement resulted, notably in the thickness of the lesions, with gradual fading of the erythematous reaction. Further treatment was not given for one month (September), and then he was given an increased oral dosage, amounting to 600 mg. daily. More rapid and progressive improvement was noted with this increased dosage. It was noteworthy that the facial lesions responded more rapidly than the lesions on the dorsa of the hands and extensor aspects of the arms. Continued progressive change has been recorded not too well.

Report of Biopsy.—A specimen, taken on June 12, consisted of full thickness of skin (fig. 3). The epidermis was generally smooth and marked by mild

hyperkeratosis and patchy parakeratosis. The pilosebaceous follicles were dilated and plugged with keratin. The granular layer was irregular in depth, and beneath the parakeratotic zones it was absent. There was general widening of the epidermis

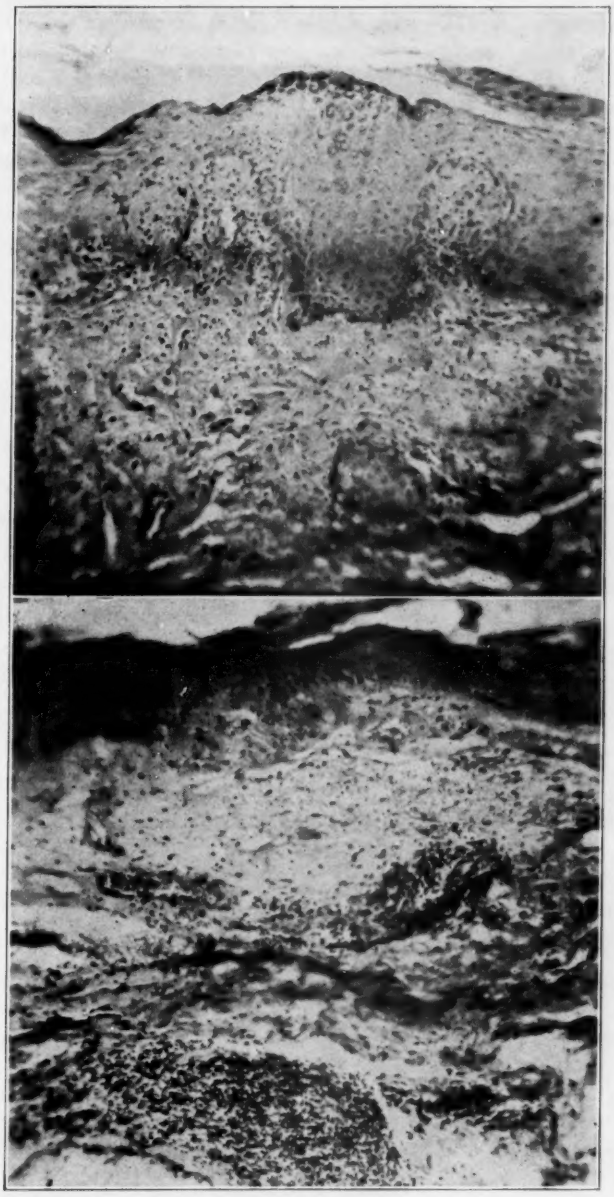

Fig. 3 (case 10).—Biopsy specimens taken June 12, 1947, before treatment.

and enlargement of its cells, and the follicles were widened, but here and there over the papillae the epidermis was much thinner. The rete pegs generally were shortened and in places absent. The zona papillaris and the zona subpapillaris in

part of the section showed coarse trabeculation of homogenized collagen, well defined telangiectasis and diffuse mild lymphocytic infiltration. In another part of the section the subpapillaris was edematous and more heavily infiltrated with lymphocytes concentrated in the perivascular position, where there was some diapedesis of red cells. Along one of the follicles, at the level of the sebaceous glands, there was a large circumscribed area of intense lymphocytic infiltration. The collagen in the remainder of the corium was well preserved.

A biopsy specimen, taken on October 23, (fig. 4), consisted of full thickness skin removed from a point adjacent to the site of the previous specimen (the angle of the jaw) and showed moderate hyperkeratosis with enlargement and plugging of the follicles. There was general narrowing of the epidermis. The rete pegs were irregularly developed. The zona papillaries showed normal finely reticulated collagens and practically no capiallary ectasia. In the upper part of the zona reticularis there were numerous dilated vessels, about which there was

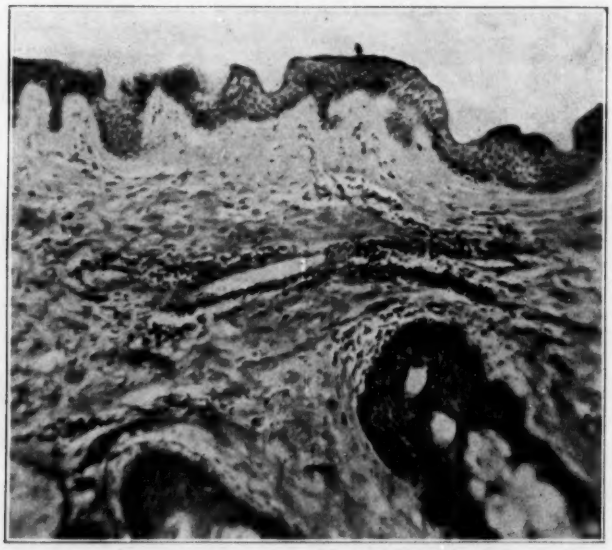

Fig. 4 (case 10).—Biopsy specimen taken Oct. 23, 1947, after treatment with tocopherols.

lymphocytic infiltration. In other places the hyperkeratosis was still apparent, the epidermis was irregularly thickened and the follicles were widened. There was still moderate ectasia of the vessels of the zona papillaris. The collagen of this zone showed a rather coarsely reticulated structure, the collagen bundles of which were swollen and homogenized, and there was a diffuse moderate lymphocytic infiltration. In the upper part of the zona reticularis there were dilated venules and areas of intense lymphocytic infiltration. Still other areas showed decided edema of the zona papillaris and the upper part of the zona reticularis.

Case 11.—Miss H. C., aged 25 (in 1934), showed particularly disfiguring lupus erythematosus, involving the nose, ears, and cheeks and consisting of fixed scaly thickened superficially atrophic patches. She also had lesions on the back and upper arms. She had had seven attacks of pneumonia, and following the last, in 1933, the lesions had developed. She then showed evidence of bronchiectatic cavity,

which had persisted over the years. She was pale, anemic and always in poor condition. In the thirteen years prior to 1947, she had had injections with bismuth and gold compounds, penicillin in large doses, sulfonamide drugs and other forms of treatment, with little value, although in 1935 she showed some slight improvement after treatment with gold compound. In May 1947, she came to us for tocopherol therapy. A small lesion on the back was partially removed, so as to leave half the lesion for future investigation. She received 1,750 mg. of mixed tocopherals intramuscularly over a four week period, during which time it was possible to see, clinically, a fading of the eruption with lessening and contraction of the lesion. Her health improved, and pain in her chest disappeared, but coughing and the amount of expectoration remained the same. Throughout the next two months she was given 300 mg. of mixed tocopherols daily by mouth, with, however, no further change in the lesions. Further injections were then given intramuscularly, without effect. Noteworthy is the fact that each injection of tocopherols produced cystlike infiltration in the muscles, a condition which was noted in another case (not of this series). She showed no further tendency toward progressive improvement, and it was felt that she had an intolerance for the tocopherols or the solvent, which prevented any utilization of tocopherols given either by mouth or by intramuscular injection. Further studies are being made in this case.

SUMMARY OF PATHOLOGIC STUDIES

The biopsies made in 3 cases (cases 6, 7 and 10) before treatment all showed lesions of lupus erythematosus, hyperkeratosis, follicular keratin plugging, thickening of the epidermis, telangiectasis of the zona papillaris and lymphocytic infiltration in the zona papillaris and the upper part of the zona reticularis. In cases 6 and 7 (figs. 1 and 2) the collagen and elastic tissue showed no appreciable changes, except for their displacement in the zones more heavily infiltrated by lymphocytes. In case 10 (fig. 3), however, there were decided collagen changes in the zona papillaris and the zona subpapillaris. Here the collagen bundles were thickened and homogenized, forming a coarse reticulated structure.

After treatment the specimens in cases 6 and 7 still showed some hyperkeratosis and follicular plugs, but the reduction in the width of the epidermis was noticeable. The telangiectasia and lymphocytic infiltration had almost disappeared. In case 10 this improvement was partial, as shown in figure 4, but there still remained considerable ectasia of the vessels and perivascular infiltration in the upper part of the zona reticularis. In other places in this same specimen of tissue (not illustrated) there were still decided hyperkeratosis and follicular plugging, widening of the epidermis, telangiectasis and lymphocytic infiltration.

COMMENT

These cases are described in some detail because of observations resulting from close and frequent clinical and histologic studies made during tocopherol therapy. Other patients, 25 in all, have been

similarly treated, and the pattern of response to treatment has closely adhered to that of the aforementioned patients.

Natural tocopherols have a definite curative value in lupus erythematosus, as shown in a study of these cases. This effect is directed at least in part toward the regeneration of the collagenous structure, as shown in the change in certain chronic infiltrative manifestations, where, prior to treatment, a degenerative state of this tissue was observed. Although the histologic changes seen in superficial nonthickened lesions of lupus erythematosus afford little suggestion as to degenerative changes within the connective tissue framework except where inflammatory cells are present, by analogy such changes are to be accepted. There is a relatively rapid disappearance of cellular infiltrations. There are coincident changes described in the epithelial layer which denote a possible specific action on the epidermal cells, apart from that on the collagenous bundles. Whether the tocopherols, in exerting this specific effect on these structures, act directly on the enzymic process within the cell body *per se* or whether the effect is produced by its known antioxidant activities through its "sparing" function[4] on vitamin A (vitamin A from diet only) cannot be further ascertained without more investigation.

Further, it is not yet possible to say whether the effect is obtained by the activity of each tocopherol acting in concerted fashion or whether alpha, beta, gamma or delta tocopherols separately have a specific function. The preponderance of alpha tocopherol in "natopherol" suggests that the specific effect of this tocopherol may be at least paramount, but there is doubt as to this.

Noteworthy is the effect of mixed tocopherol therapy in photosensitivity, a common observation in cases of lupus erythematosus. In 4 of the cases enumerated in this series, there was a history of photosensitivity, which was lost entirely following tocopherol therapy. In 1 case of photosensitivity, we had treated the patient successfully prior to this study of lupus erythematosus; it is inferred that this phenomenon of photosensitivity may be directly related to the state of the collagenous system.

It should be noted that all of these patients were treated simultaneously by the administration of the tocopherols both by mouth and parenterally, except in case 9. Either route of administration will probably give comparable results, depending on the amount absorbed. Tocopherols in natural oils produce some pain and reaction when given intramuscularly. It is our observation that bed patients have

4. Hickman, K. C. D.; Kaley, M. W., and Harris, P. L.: Covitamin Studies: I. The Sparing Action of Natural Tocopherol Concentrates on Vitamin A, J. Biol. Chem **152**:303-311 (Feb.) 1944.

little discomfort but that ambulatory patients complain of discomfort about the third or fourth day after treatment. The injection is best given into the gluteus maximus muscle about 2 or 3 inches (about 5 or 7.5 cm.) from the crest of the ilium.

Of a large number of cases (apart from cases herein presented) in which intramuscular injections of tocopherols in oil were given, tumor-like infiltrations developed in only 1 case, at the site of injection in the muscles, that have persisted over a long period of time. Some patients have presented infiltrative lesions, which have, however, gradually disappeared. In rats, intramuscular injections of mixed tocopherols result constantly in such infiltrations, from which practically 100 per cent of tocopherols have been recovered (Harris[5]). It would be wise to discontinue such injections in human beings when any permanence of infiltration presents itself. Occasionally a patient is seen who tolerates orally administered fat-soluble tocopherols rather poorly, the effect being that of gastrointestinal disturbance, headache and lassitude. Such patients have been few, and their treatment has had to be discontinued.

Except in experimental studies and observations, the tocopherols seem to give adequate values when taken by mouth. Superficial lupus erythematosus, no matter how long standing, responds with moderate dosage, 100 to 300 mg. daily. Improvement and curative progress seem to be proportionate to the amount given, and in cases of severe disease, in which there is decided marked thickening, large doses (600 mg. daily) should be given, preferably between meals and with an empty stomach. Also, there should be a reduced fat content in the diet. Hove, Hickman and Harris[6] have shown that excessive intake of fat interferes with the utilization of the tocopherols.

While the effect of the mixed tocopherols in lupus erythematosus is apparently profound, often rapid, and at times almost specific, in its effect, the fact remains that recurrences are not uncommon and that the treatment of patients should not end with the clearing up of the eruption. Biopsies have shown in several cases, when the specimen was taken long after apparent clinical cure, that detectable microscopic evidence of incomplete regression is seen which may possibly account for the recurrent clinical manifestations. Treatment should, therefore, be maintained after apparent clinical cure. Sufficient time has not yet elapsed to define this further. This is important, and at present a maintenance dose equivalent to 50 mg. of alpha tocopherol daily is advised until further knowledge as to the true relationship between

5. Harris, P. L.: Personal communication to the authors.

6. Hove, E. L.; Hickman, K. C. D., and Harris, P. L.: The Effect of Tocopherol and of Fat on the Resistance of Rats to Anoxic Anoxia, Arch. Biochem. **8**:395-404 (Dec.) 1945.

the tocopherols and the connective tissue ground substance is forthcoming.

SUMMARY AND CONCLUSIONS

A series of cases in which mixed tocopherols were employed in the treatment for lupus erythematosus is reported, in which some favorable curative effects have been obtained. Superficial lesions clear up quickly with this form of treatment. Deep infiltrative lesions require more intensive and prolonged treatment, and the results, while not so spectacular as in the superficial type of disease, are progressive. In a series of 25 cases, 1 patient with long-standing disease and with decided infiltration showed early improvement and then failed to respond to tocopherol therapy. While this report largely deals with the effect of the administration of tocopherols for lupus erythematosus, it is not considered that other aspects of investigation, such as the factor of infection, should be ignored.

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PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

IV. The Synergistic or Additive Activity of Penicillin by Oral Administration with Oxophenarsine Hydrochloride ("Mapharsen") by Intravenous and Intramuscular Injection and Bismuth Salicylate by Intramuscular Injection

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UNDOUBTEDLY the administration of penicillin by intramuscular injection along with oxophenarsine hydrochloride ("mapharsen") intravenously has resulted in pronounced synergistic or additive effects in the treatment of experimental syphilis of rabbits.[1] Similar synergistic or additive effects have also been observed in combined treatment with penicillin and bismuth compound by intramuscular injection.[1b]

However, since penicillin by oral administration is much less effective than by intramuscular injection in the treatment of experimental syphilis of rabbits,[2] the purpose of this investigation was to determine the possible synergistic or additive activity of the compound by oral administration in conjunction with the administration of oxophenarsine hydrochloride by intravenous and intramuscular injection and of bismuth salicylate by intramuscular injection. Thus, while penicillin given orally in a dosage of 500 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 units per kilogram of body weight, has yielded temporarily negative results in dark field examinations for Treponema pallidum,

From the Research Institute of Cutaneous Medicine, Philadelphia.

1. (*a*) Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946. (*b*) Kolmer, J. A.: Studies on Penicillin in the Treatment of Experimental Syphilis of Rabbits: II. The Synergistic or Additive Activity of Penicillin, Mapharsen (Oxophenarsine Hydrochloride) and Potassium Bismuth Tartrate, Arch. Dermat. & Syph. **56**:179 (Aug.) 1947.

2. Kolmer, J. A.: Studies of Penicillin in the Treatment of Experimental Syphilis of Rabbits: III. The Therapeutic Activity of Penicillin by Oral Administration, Arch. Dermat. & Syph. **56**:344 (Sept.) 1947.

complete or biologic cure required the administration of as much as 15,000 to 20,000 units per kilogram of body weight three times a day for ten days in succession, totaling 450,000 to 600,000 units per kilogram of body weight. The results of this investigation have shown, however, that the oral administration of 500 to 1,000 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 to 30,000 units per kilogram of body weight, was completely curative in conjunction with subcurative doses of oxophenarsine hydrochloride or bismuth compound given parenterally.

METHODS AND MATERIALS

Rabbits were inoculated intratesticularly with the Nichols-Hough strain of Treponema pallidum. Acute orchitis developed in all, with strongly positive results in dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total of seventy days. At the expiration of that time the popliteal lymph nodes of all treated animals were injected into the testicles of fresh animals; these animals were kept under observation for a minimum of four months, when the results were evaluated.

The penicillin was that previously employed,[2] being a commercial amorphous sodium salt with an assay potency of 544 units per milligram, containing 88 per cent of penicillin G (supplied by the Commercial Solvents Corporation [lot No. 45072102]). Solutions for administration were freshly prepared in isotonic solution of sodium chloride containing 2,000 units per cubic centimeter.

Anhydrous sodium citrate was employed as an antacid. Solutions were prepared in distilled water containing 0.1 Gm. per cubic centimeter. For administration the dose of penicillin per kilogram of body weight was mixed with 2 cc. of the citrate solution (0.2 Gm.) and given by stomach tube to fasting rabbits at 9 a.m., 1 p.m. and 3 p.m. on each of ten days in succession, totaling thirty doses for each animal.

In one experiment oxophenarsine hydrochloride dissolved in sterile isotonic solution of sodium chloride was given intravenously once a day for ten days in succession, along with penicillin by oral route. In a second experiment oxophenarsine hydrochloride was suspended in a mixture of sterile peanut oil and 3 per cent wax (5 mg. per cubic centimeter) and given on the second, fourth, sixth and eighth days of treatment by intramuscular injection, along with penicillin by the oral route. In a third experiment bismuth salicylate in peanut oil (Parke, Davis & Company) was diluted with sterile peanut oil (5 mg. per cubic centimeter) and given on the second, fourth, sixth and eighth days of treatment by intramuscular injection, along with penicillin by oral route.

RESULTS OBSERVED

Penicillin by Oral Administration with Oxophenarsine Hydrochloride by Intravenous Injection.—As shown in table 1, the single minimal curative dose of oxophenarsine hydrochloride given by intravenous injection was 8 to 10 mg. per kilogram of body weight,

being similar to the results reported by Probey,[3] who observed the single minimal effective dose to be about 8 mg. per kilogram of body weight. When administered intravenously once a week for eight weeks in succession the total minimal curative dose was about 16 mg. per kilogram of body weight.

As shown in table 2, oxophenarsine hydrochloride given in a dosage of 0.5 mg. per kilogram of body weight by intravenous in-

TABLE 1.—*Oxophenarsine Hydrochloride by Intravenous Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

Experiment No.	Dose (Mg. per Kilogram of Body Weight)	No. of Doses	Results of Dark Field Examination for T. pallidum: Days*												Results of Lymph Node Transfers
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	2.0	1	4	1	—	—	—	—	—	—	—	—	—	—	—	Positive
2	2.0	1	4	2	1	—	—	—	—	—	—	—	—	—	—	Positive
3	4.0	1	4	1	—	—	—	—	—	—	—	—	—	—	—	Positive
4	4.0	1	4	1	—	—	—	—	—	—	—	—	—	—	—	Positive
5	6.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Positive
6	6.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Positive
7	8.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Positive
8	8.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
9	10.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
10	10.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
11	0.5	8†	4	4	4	4	4	4	—	—	—	—	—	—	—	Positive
12	0.5	8	4	4	4	4	4	4	1	—	—	—	—	—	—	Positive
13	1.0	8	4	1	1	2	1	—	—	—	—	—	—	—	—	Positive
14	1.0	8	4	2	1	2	2	—	—	—	—	—	—	—	—	Positive
15	2.0	8	4	1	1	—	—	—	—	—	—	—	—	—	—	Negative
16	2.0	8	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
17	4.0	8	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
18	4.0	8	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative

*After institution of treatment; 4=large numbers of actively motile spirochetes per dark field; 3, 2 and 1=smaller number of spirochetes per dark field; — = negative results in dark field examinations.

†Once a week for eight weeks in succession.

jection once a day for ten days in succession, totaling 5 mg, per kilogram of body weight, was not completely curative. Likewise, penicillin by oral administration, in doses of 500, 1,000, 5,000 and 10,000 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 to 300,000 units per kilogram of body weight,

3. Probey, T. F.: Comparison of the Spirochetal Activity of Arsphenamines and Phenarsines (Arsenoxides) in Experimental Syphilis, Pub. Health Rep. **62**:1041 (July) 1947.

was not completely curative. But penicillin by oral administration given in a dosage of 500 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 units per kilogram of body weight, in conjunction with daily intravenous injections of oxophenarsine hydrochloride in a dosage of 0.5 mg. per kilo-

TABLE 2.—*Penicillin by Oral Administration with Oxophenarsine Hydrochloride by Intravenous Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

Experiment No.	Oxophenarsine Hydrochloride*		Penicillin†		Results of Dark Field Examination for T. Pallidum: Days‡												Results of Lymph Node Transfers
	Dose	Tot.	Dose	Total	1	2	3	7	14	21	28	35	42	49	56	63	70	
1	0.5	5.0	—	—	4	4	2	—	—	—	2	4	4	4	4	4	4	Positive
2	0.5	5.0	—	—	4	4	1	1	—	—	—	4	4	4	4	4	4	Positive
3	—	—	500	15,000	2	2	—	—	3	4	4	4	4	4	4	4	4	Positive
4	—	—	500	15,000	2	1	1	—	2	4	4	4	4	4	4	4	4	Positive
5	—	—	1,000	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
6	—	—	1,000	30,000	1	1	—	—	—	—	—	—	—	—	—	—	—	Positive
7	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
8	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
9	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
10	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
11	0.5	5.0	500	15,000	4	4	3	—	—	—	—	—	—	—	—	—	—	Negative
12	0.5	5.0	500	15,000	4	4	4	—	—	—	—	—	—	—	—	—	—	Negative
13	0.5	5.0	500	15,000	4	4	2	—	—	—	—	—	—	—	—	—	—	Negative
14	0.5	5.0	1,000	30,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Negative
15	0.5	5.0	1,000	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
16	0.5	5.0	1,000	30,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Negative
17	0.5	5.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
18	0.5	5.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
19	0.5	5.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative

*Milligrams per kilogram of body weight, once a day for ten days in succession by intravenous injection.

†Units per kilogram of body weight, three times a day for ten days in succession by oral administration.

‡After institution of treatment; 4=large numbers of actively motile spirochetes per dark field; 3, 2 and 1=smaller numbers of spirochetes per dark field; — = negative results in dark field examinations.

gram of body weight, totaling 5 mg. per kilogram of body weight, was completely curative. Smaller doses of penicillin were not employed because such decided synergistic or additive effects were not expected when the experiment was undertaken. Larger doses of penicillin by oral administration, totaling 30,000 and 150,000 units per kilogram of body weight, along with oxophenarsine hydrochloride in a total dosage of 5 mg. per kilogram of body weight, given by intravenous injection, also resulted in complete or biologic cure.

Penicillin by Oral Administration with Oxophenarsine Hydrochloride by Intramuscular Injection.—As previously reported,[4] the single maximum tolerated dose of oxophenarsine hydrochloride suspended in sterile peanut oil given by intramuscular injection to rats was about 200 mg. per kilogram of body weight. The single minimal curative dose in the treatment of acute syphilitic orchitis of rabbits was about 15 mg. per kilogram of body weight. Only minor degrees

TABLE 3.—*Oxophenarsine Hydrochloride in Peanut Oil and Wax by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

Experiment No.	Dose (Mg. per Kilogram of Body Weight)	No. of Doses	Results of Dark Field Examination for T. Pallidum: Days*													Results of Lymph Node Transfers
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	5.0	1	4	1	—	—	4	4	4	4	4	4	4	4	4	Positive
2	5.0	1	4	2	—	—	4	4	4	4	4	4	4	4	4	Positive
3	10.0	1	4	1	—	—	—	—	—	—	—	—	—	—	—	Positive
4	10.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Positive
5	15.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Positive
6	15.0	1	4	1	—	—	—	—	—	—	—	—	—	—	—	Positive
7	20.0	1	3	—	—	—	—	—	—	—	—	—	—	—	—	Negative
8	20.0	1	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
9	1.0	8†	4	4	4	4	1	4	1	—	—	—	—	—	2	Positive
10	1.0	8	4	4	4	4	2	4	2	—	—	—	—	—	3	Positive
11	2.0	8	4	4	4	1	—	—	—	—	—	—	—	—	2	Positive
12	2.0	8	4	4	4	—	—	—	—	—	—	—	—	—	2	Positive
13	5.0	8	4	4	—	—	—	—	—	—	—	—	—	—	—	Negative
14	5.0	8	4	2	—	—	—	—	—	—	—	—	—	—	—	Negative
15	10.0	8	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
16	10.0	8	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative

*After institution of treatment; 4=large numbers of actively motile spirochetes per dark field; 3, 2 and 1=smaller numbers of spirochetes per dark field; — =negative results in dark field examinations.

†Once a week for eight weeks in succession.

of inflammatory reactions, characterized by slight leukocytic infiltrations without necrosis, were observed on histologic examination of specimens excised at the sites of injection in rats ten days after intramuscular injections of 40 mg. per kilogram of body weight.

In this investigation the maximum tolerated dose of oxophenarsine hydrochloride suspended in sterile peanut oil and 3 per cent wax given by intramuscular injection to rats was about 220 mg. per

4. Brown, H., and Kolmer, J. A.: The Toxicity and Therapeutic Effectiveness of Mapharsen by Intramuscular Administration, Am. J. Syph., Gonor. & Ven. Dis. **27**:488 (July) 1943.

kilogram of body weight. Specimens excised at the sites of injection ten days after intramuscular injections of 40 mg. per kilogram of body weight and examined histologically showed about the same degrees of slight leukocytic infiltrations without necrosis as observed following intramuscular injections of 40 mg. per kilogram of body weight of the compound suspended in sterile peanut oil alone.

TABLE 4.—*Penicillin by Oral Administration with Oxophenarsine Hydrochloride by Intravenous Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

Experiment No.	Oxophenarsine Hydrochloride*		Penicillin†		Results of Dark Field Examination for T. Pallidum: Days‡												Results of Lymph Node Transfers
	Dose	Tot.	Dose	Total	1	2	3	7	14	21	28	35	42	49	56	63	70	
1	1.0	4.0	—	—	4	4	2	—	—	—	—	2	4	4	4	4	4	Positive
2	1.0	4.0	—	—	4	2	2	—	—	—	—	2	4	4	4	4	4	Positive
3	—	—	500	15,000	2	1	—	—	2	4	4	4	4	4	4	4	4	Positive
4	—	—	500	15,000	2	2	1	—	3	4	4	4	4	4	4	4	4	Positive
5	—	—	1,000	30,000	2	1	1	—	—	—	—	—	—	—	—	—	—	Positive
6	—	—	1,000	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
7	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
8	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
9	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
10	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
11	1.0	4.0	500	15,000	4	1	—	—	—	—	—	—	—	—	4	4	4	Positive
12	1.0	4.0	500	15,000	4	2	—	—	—	—	—	—	—	2	4	4	4	Positive
13	1.0	4.0	500	15,000	4	1	—	—	—	—	—	—	—	—	4	4	4	Positive
14	1.0	4.0	1,000	30,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
15	1.0	4.0	1,000	30,000	4	2	—	—	—	—	—	—	—	—	—	—	—	Negative
16	1.0	4.0	1,000	30,000	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
17	1.0	4.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
18	1.0	4.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
19	1.0	4.0	5,000	150,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative

*Milligrams (per kilogram of body weight) in peanut oil and wax on the second, fourth, sixth and eighth days of treatment by intramuscular injection.

†Units per kilogram of body weight, three times a day for ten days in succession by oral administration.

‡After institution of treatment; 4=large numbers of actively motile spirochetes per dark field; 3, 2 and 1=smaller numbers or spirochetes per dark field; — =negative results in dark field examinations.

As shown in table 3, the single minimal curative doses of oxophenarsine hydrochloride suspended in peanut oil and wax was about 20 mg. per kilogram of body weight, or twice the single minimal curative dose of the compound administered by intravenous injection. When injected once a week for eight weeks in succession, the total minimal curative dose was about 40 mg. per kilogram of body weight.

As shown in table 4, oxophenarsine hydrochloride suspended in peanut oil and in wax in a dosage of 1 mg. per kilogram of body weight, given by intramuscular injection, on the second, fourth, sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight, was not completely curative. Likewise, penicillin by oral administration in doses of 500, 1,000, 5,000 and 10,000 units per kilogram

TABLE 5.—*Penicillin by Oral Administration with Bismuth Compound by Intramuscular Injection in the Treatment of Acute Syphilitic Orchitis of Rabbits*

Experiment No.	Bismuth Salicylate*		Penicillin†		Results of Dark Field Examination for T. Pallidum: Days‡												Results of Lymph Node Transfers
	Dose	Tot.	Dose	Total	1	2	3	7	14	24	28	35	42	49	56	63	70	
1	1.0	4.0	—	—	4	4	4	2	—	—	3	4	4	4	4	4	4	Positive
2	1.0	4.0	—	—	4	4	4	1	—	—	1	4	4	4	4	4	4	Positive
3	—	—	500	15,000	2	2	—	—	2	4	4	4	4	4	4	4	4	Positive
4	—	—	500	15,000	2	2	—	—	4	4	4	4	4	4	4	4	4	Positive
5	—	—	1,000	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
6	—	—	1,000	30,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Positive
7	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
8	—	—	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Positive
9	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
10	—	—	10,000	300,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Positive
11	1.0	4.0	500	15,000	4	—	—	—	—	—	—	—	—	—	—	—	—	Negative
12	1.0	4.0	500	15,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
13	1.0	4.0	500	15,000	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
14	1.0	4.0	1,000	30,000	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
15	1.0	4.0	1,000	30,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
16	1.0	4.0	1,000	30,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
17	1.0	4.0	5,000	150,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
18	1.0	4.0	5,000	150,000	4	1	—	—	—	—	—	—	—	—	—	—	—	Negative
19	1.0	4.0	5,000	150,000	2	—	—	—	—	—	—	—	—	—	—	—	—	Negative

*Milligrams (per kilogram of body weight) of bismuth salicylate in peanut oil given on the second, fourth, sixth and eighth days of treatment by intramuscular injection.

†Units per kilogram of body weight, three times a day for ten days in succession by oral administration.

‡After institution of treatment; 4=large numbers of actively motile spirochetes per dark field; 3, 2 and 1=smaller numbers of spirochetes per dark field; — =negative results in dark field examinations.

of body weight three times a day for ten days in succession, totaling 15,000 to 300,000 units per kilogram of body weight, was not completely curative. However, penicillin by oral administration in a dosage of 1,000 units per kilogram of body weight three times a day for ten days in succession, totaling 30,000 units per kilogram of body weight, in conjunction with intramuscular injections of oxophenarsine hydrochloride suspended in peanut oil and wax given in a dosage

of 1 mg. per kilogram of body weight on the second, fourth, sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight, was completely curative. Larger doses of penicillin by oral administration, totaling 150,000 units per kilogram of body weight, along with oxophenarsine hydrochloride given in a total dosage of 4 mg. per kilogram of body weight by intramuscular injection, also resulted in complete or biologic cure.

Penicillin by Oral Administration with Bismuth Salicylate Given by Intramuscular Injection.—The single minimal curative dose of bismuth salicylate suspended in peanut oil given by intramuscular injection is from 10 to 15 mg. per kilogram of body weight. As shown in table 5, intramuscular injections of 1 mg. per kilogram of body weight, given on the second, fourth, sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight, were not completely curative. Likewise, penicillin by oral administration in dosages of 500, 1,000, 5,000 and 10,000 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 to 30,000 units per kilogram of body weight, was not completely curative. However, penicillin by oral administration in a dosage of 500 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 units per kilogram of body weight, in conjunction with intramuscular injections of bismuth salicylate given in a dosage of 1 mg. per kilogram of body weight on the second, fourth, sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight, was completely curative. Smaller doses of penicillin were not employed because such decided synergistic or additive effects were not expected when the experiment was undertaken. Larger doses of penicillin by oral administration, totaling 30,000 and 150,000 units per kilogram of body weight, along with bismuth salicylate given in a total dosage of 4 mg. per kilogram of body weight by intramuscular injection, also resulted in complete or biologic cure.

COMMENT

Since the curative activity of penicillin by oral administration in experimental syphilis is so much less than by intramuscular injection in isotonic solution of sodium chloride and peanut oil and wax, the oral administration of the compound alone is apparently contraindicated in the treatment for both early and late syphilis in human beings.

The results of this investigation, however, indicate that the curative activity of penicillin by oral administration in the treatment of experimental syphilis is materially enhanced when given in conjunction with oxophenarsine hydrochloride by intravenous or intra-

muscular injection; this is also true of penicillin administered in conjunction with bismuth salicylate by intramuscular injection. Whether or not similar synergistic or additive effects of penicillin given orally, in conjunction with oxophenarsine hydrochloride and bismuth compound given by parenteral injection, occur in the treatment of syphilis in human beings cannot be stated, although it is probably worthy of investigation, especially in the treatment of late acquired and congenital syphilis.

Incidentally, one may again refer to the administration by intramuscular injection of oxophenarsine hydrochloride suspended in peanut oil or peanut oil and wax as a more potent compound than sulfarsphenamine given by subcutaneous or intramuscular injection in the treatment of congenital syphilis of infants or young children and in adults with veins which are difficult to penetrate. As reported five years ago,[4] the compound suspended in sterile peanut oil given by intramuscular injection is well borne, with but slight local reactions, in rats, and the same observation has been made in this investigation with respect to suspensions in peanut oil and wax. According to Probey,[3] the single minimal curative dose of sulfarsphenamine in isotonic solution of sodium chloride given by intramuscular injection, in the treatment of experimental syphilis, is about 40 mg. per kilogram of body weight. According to the results of my investigations, the single minimal curative dose of oxophenarsine hydrochloride suspended in peanut oil is about 15 mg. per kilogram of body weight and in peanut oil and wax it is about 20 mg. per kilogram of body weight.

SUMMARY

Penicillin given orally three times a day for ten days in succession, totaling 15,000 to 300,000 units per kilogram of body weight, was not completely curative in the treatment of experimental syphilis in rabbits. However, the oral administration of 500 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 units per kilogram of body weight, was completely curative in conjunction with daily intravenous injection of oxophenarsine hydrochloride ("mapharsen") in a dosage of 0.5 mg. per kilogram of body weight, totaling 5 mg. Oxophenarsine hydrochloride given alone in this dosage was not completely curative.

Penicillin given orally in a dosage of 1,000 units per kilogram of body weight three times a day for ten days in succession, totaling 30,000 units per kilogram of body weight, was completely curative in infected rabbits in conjunction with oxophenarsine hydrochloride suspended in peanut oil and given in a dosage of 1 mg. per kilogram of body weight by intramuscular injection, on the second, fourth,

sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight. Oxophenarsine hydrochloride alone given in this dosage was not completely curative.

Penicillin given orally in a dosage of 500 units per kilogram of body weight three times a day for ten days in succession, totaling 15,000 units per kilogram of body weight, was completely curative in conjunction with bismuth salicylate given in a dosage of 1 mg. per kilogram of body weight by intramuscular injection on the second, fourth, sixth and eighth days of treatment, totaling 4 mg. per kilogram of body weight. Bismuth salicylate alone given in this dosage was not completely curative.

The advisability of determining the possible synergistic or additive activity of penicillin by oral administration in conjunction with the parenteral administration of oxophenarsine hydrochloride and bismuth compound in the treatment of late acquired and congenital syphilis is briefly discussed; the same results were obtained in the clinical trial of oxophenarsine hydrochloride suspended in peanut oil or peanut oil and wax given by intramuscular injection in the treatment of syphilis, especially congenital syphilis.

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CAUSATIVE DIAGNOSIS OF CONTACT DERMATITIS

II. A Classification of Patterns on the Hands

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ONE OF the means of establishing the causation of contact dermatitis is the careful observation of the localization and of the exact outline of the lesion. Many contacts responsible for dermatitis produce characteristic designs. Significant as they are, little attention has been focused on them in the past. Wise and Sulzberger[1] first presented a classification of typical sites, and one of us (Waldbott[2]) has established a series of diagrams depicting typical localizations of dermatitis on the surface of the whole body. It was impossible to incorporate details about the hands in these diagrams. Yet, dermatitis of the hands is not only common, but its causes are by far the most difficult to determine. It is, therefore, desirable to present a classification of contact dermatitis of the hands according to the pattern of the lesions.

METHOD

Photographs taken of lesions in 51 cases formed the basis of this study. Because of war restrictions of photographic materials, exact drawings of the distribution of the lesions were substituted in 34 additional cases the lesions in which could not be photographed.[3] In order to familiarize ourselves more thoroughly with the patterns produced by the various contacts, fingerprint ink was applied to the objects to be handled. When the object was gripped in the usual manner, the ink was transferred to the hand, and the pattern thus produced was photographed.

1. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1935, p. 6.

2. Waldbott, G. L.: Localization: An Aid in the Diagnosis of Contact Dermatitis, J. Michigan M. Soc. **41**:392-397 (May) 1942.

3. This study was further stimulated by the work of Ronchese.[5] His problem, identifying occupational marks, closely resembles ours. In his exhibit at the American Medical Association convention in 1946, a number of designs and photographs of contact dermatitis were found, the use of which he permitted for this study. We also inspected the photographic files of the following dermatologists: Dr. M. B. Sulzberger, New York; Dr. Arthur Curtis, Ann Arbor, Mich., and Dr. Arthur Schiller, Detroit.

The classification of this material was difficult. After investigating several methods of cataloguing the designs, a classification was adopted based chiefly on the object which was responsible for the lesion. We thus followed a custom of some clinicians who have been speaking, for instance, of "soap" dermatitis or "glove type" dermatitis. The main subdivisions were based on the anatomy of the hands. It is impossible to present at this time a final all-inclusive classification. This report should therefore be considered a preliminary one. However, in its present state it forms the framework for future modifications and additions. The purpose of this preliminary presentation is to aid in the detection and cataloguing of new causative agents.

DIAGNOSIS

First, some points concerning the morphologic aspect of dermatitis will be discussed briefly. It is generally recognized that contact dermatitis does not always retain its original appearance (Stokes, Lee and Johnson[4]). It may become modified by secondary contact sensitizations, especially from drugs, if ointments are applied, or through atopic sensitizations in allergic persons, namely, through inhalation of air-borne substances or ingestion of food to which sensitivity exists. If fluid or semifluid agents, such as oils, creams or soaps, are responsible for the dermatitis, the original design tends to spread beyond its primary site. Furthermore, the causative substance may produce irritation through its chemical action as well as dermatitis through contact, as, for instance, in lesions from gasoline or from certain drugs. If the condition is chronic, hyperkeratosis and callus formation may camouflage the underlying contact lesion. More frequently, secondary impetigo, suppurative lesions, fungous (especially monilia) infections and lymphadentitis become superimposed on the area manifesting originally the "venenata type" of dermatitis. Regardless of these possible variations in the appearance of the lesion, a characteristic pattern is detectable for each contact, and, vice versa, the design furnishes a clue as to the cause of the lesion.

CLASSIFICATION

It is not within the scope of this paper to discuss the various chemicals present in the articles responsible for the dermatitis. In our series, which did not include cases of industrial dermatitis, nickel, dyes, varnishes, plastics and rubber were mostly responsible. A certain object occasionally produces more than one design, because there are various modes of gripping it. It may therefore appear under several headings in this classification. The power of the grip, the shape of the hand and the size and consistency of the object, influence the ex-

4. Stokes, J. H.; Lee, W. E., and Johnson, H. M.: Contact, Contact-Infective and Infective-Allergic Dermatitis of Hands, with Special Reference to Rubber Glove Dermatitis, J.A.M.A. **123**:195-202 (Sept. 25) 1943.

tent of the design. Such variations are readily recognizable after one has become familiar with the general pattern of the contact.

Following the order of frequency in which the lesions were encountered, those appearing on the volar surface of the hands are con-

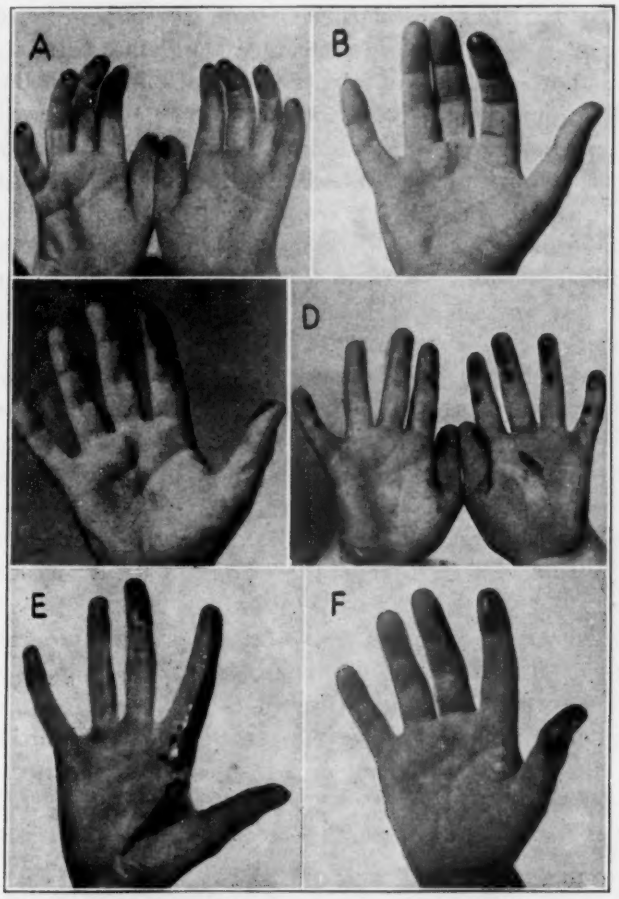

FIG. 1.—Contact dermatitis. Finger tip type: *A*, due to contact with typewriter keys, and *B*, due to contact with the push buttons of a radio. Other sources of similar patterns are piano keys, violin strings, harp strings, organ keys, wave set lotion, hair tonic, eye ointment, starter of a car, electric bell buttons, wood wind instruments, brass instruments and rubber hair curlers. Finger grip type: *C*, due to contact with a radio dial, and *D*, due to contact with playing cards. Other sources of similar patterns are safe dials, keys, caps of tubes of tooth paste, watch stems, water faucets, radiator valves, lipstick containers, electric light switches, gear shift levers, light chains, hair pins, celery, radishes, olives, peanuts, popcorn, pills, tablets and screw drivers. Other designs on the fingers: *E*, due to contact with an open box, and *F*, due to contact with an ash tray. Other sources of similar patterns are manicure outfits and paper bags.

sidered first, those on both volar and dorsal surfaces are considered next, and those on the dorsal surface only are taken up last.

A. Volar Group.—Dermatitis on the volar surface is classified

according to whether the lesions are present on the fingers only, on the fingers and the palm, or on the palm.

1. Fingers (fig. 1): (*a*) Finger tip type. These lesions are relatively easy to identify, since the contacts are limited to objects similar to typewriter, piano or organ keys. Ronchese[5] described and illustrated occupational marks in musicians from the strings of violins and harps, the wood of wood wind instruments and the metal of certain brass instruments. We encountered 2 such cases, in which there were callous formations which we felt, but were unable to prove, were superimposed on primary contact dermatitis. A beauty parlor operator, with dermatitis on both hands, exhibited considerable irritation on the finger tips due to massaging a certain hair tonic into the scalp of his clients. In another person, the use of rubber hair curlers was responsible for lesions on the finger tips. Another patient, with dermatitis on both eyelids, showed small areas on the tips of the third and fourth fingers of both hands. Merthiolate was responsible for the lesions both on the eyes and on the finger tips. Pulling down the eyelids when applying the drops led to contact of the liquid with the finger tips. Irritations from ointments and liquids can be distinguished from those from solid articles since they favor the areas beneath and around the nails.

Lesions on individual fingers originate from the touch of a plastic or metal button, such as that of the starter of a car, a radio or an electric bell.

(*b*) Finger and grip type. A typical pattern arises on the distal portion of the first three or four fingers of the right hand (or left in left-handed persons). This is the result of picking up certain foods, such as celery or popcorn, or certain pills and tablets, touching such objects as the knob of a file case or a lipstick container, turning on a switch, holding onto the lever of a gear shift and similar contacts. If the object is small, as, for instance, the chain (nickel) of a light or a hair pin (lacquer), small patches appear on the adjoining surfaces of the index and middle fingers and on the volar area of the thumb. If the agent is larger, the lesions tend to spread onto the lower portions of these three fingers and to the lateral aspect of the ring finger. This is particularly true when there is a turning or twisting motion, as in turning a key or the knob of a radio, a door or a safe or in using a screw driver.[6] Unscrewing the cap of a tube of tooth paste accounts for small patterns and habitually turning a water faucet or a radiator valve for larger ones.

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5. Ronchese, F.: Calluses, Cicatrices and Other Stigmas as an Aid to Personal Identification, J.A.M.A. **128**:925-932 (July 28) 1945.

6. Screw drivers produce an additional contact in the center of the palm.

In this group of lesions affecting the volar surfaces of the fingers only, those from holding a rotogravure newspaper and from the use of a plastic knitting needle should also be mentioned.

A slight variation from the "finger grip" type is the pattern originating from the habitual gripping of an open box, such as a cash box, a plastic ash tray or a plastic manicure outfit ("open box" type). In these instances, the medial aspect and the base of the thumb are the sites of irritation.

2. Fingers and Palm: The involvement of both the palm and the volar surface of the fingers is common. While there is a general resemblance in all these designs, it is possible to distinguish three separate types.

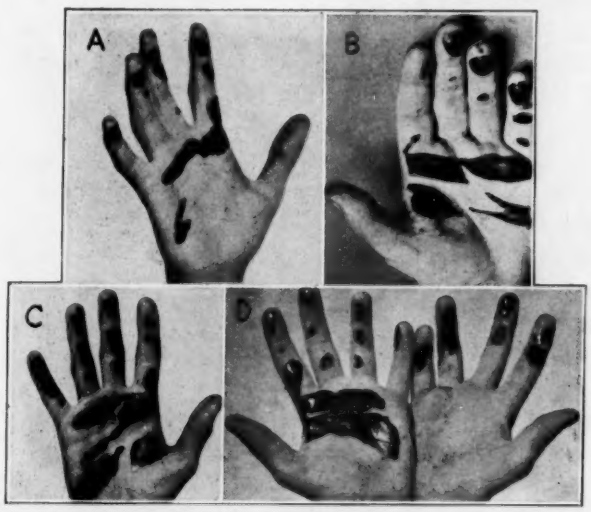

FIG. 2.—Contact dermatitis. Bar type (horizontal grip): *A*, due to contact with a sturdy rope, and *B*, due to contact with a bar. Other sources of similar patterns are knife handles, rubber hose, dog leaches, bridle straps, wire, books, tooth brushes and handbag straps. *C*, Z type (oblique grip), due to contact with an athlete's bar, and *D*, due to contact with a steering wheel. Other sources of similar patterns are tennis racquets, saw handles, electric irons, large knife handles, bicycle grips, handles of pans, golf clubs, hand mirrors and vacuum cleaners, horse radish and carrots.

(*a*) Horizontal bar type (fig 2). This results from gripping a bar in a horizontal position, as encountered in gymnastics, or from grasping other elongated objects, such as a rope. The lower portions of four fingers as well as the opposite areas on the distal surface of the hand are primarily in contact with the object. The thicker the bar, the more the pattern extends into the hand. Lesions from such contacts further vary somewhat with the tightness of the grip and the shape of the hand. If the hand is of a long and angular shape rather than short and stocky, the Z type design, described subsequently, is likely to arise. The more tightly the object is held, the more does the

web space between the index finger and thumb as well, as the medial surface of the thumb, become involved. Examples of the "horizontal bar" type are lesions from a tooth brush, comb, metal or insulated wire, rope, strap of a handbag, dog leash and bridle strap. More extensive irritations occur from habitual handling of a knife with a (cocobola) wooden handle or a rubber hose.

(*b*) "Oblique bar" grip (Z type). If the bar is held in an oblique or vertical position instead of at right angles to the fingers, a distinct-

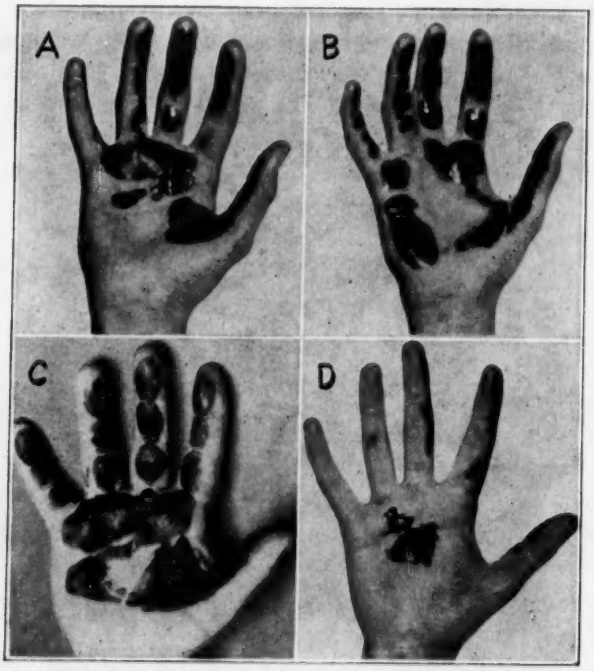

FIG. 3.—Contact dermatitis. Ball type: *A*, due to contact with an article of the small ball type, and *B*, of the medium ball type. The small ball type may be due to handling limes, cigaret lighters, pocket knives, match boxes, key cases, door knobs and electric razors. The medium ball patterns may be due to handling items such as tin cans and oranges. *C*, the large ball type of pattern may result from handling grapefruit, footballs, large rubber balls and cocktail shakers. *D*, illustrates the central palm type, with the typical pattern resulting from the handling of a screw driver. Other sources of similar pattern are knobs of canes, platen knobs (typewriter), tooth paste, tooth powder, condiments, powdered food substances, gear shift knobs (old-fashioned type) and soap dispensers.

ly different pattern can be discerned, which occasionally has the shape of a "Z". This pattern is most distinct if the grip is tight, as in dermatitis from the leather dye of golf clubs. The upper part of the Z is formed by the distal part of the palm; the lower part reaches from the base of the thumb toward the hypothenar eminence. Other objects which can be easily identified with this design are the tennis racket (leather, leather dye), bicycle grip (plastic, rubber), handle of a

saw (varnish, wood), steering wheel (plastic) and handle of an electric iron.

Slight modifications of the Z type are encountered when the end of the bar is held in the hand, as in gripping the rubber end of a vacuum cleaner or the end of the handle of a pan, a hand mirror or a large-sized knife. In this case the central portion of the palm manifests lesions of dermatitis. A design with this distribution was observed on the left hand of a woman from peeling horse radish.

(*c*) Ball type (fig. 3). A ball or ball-like object gives rise to two rather distinct designs, depending on its size. A football, a large rubber ball or a grapefruit (rind) is likely to irritate the whole inside surface of the hand except for some areas in the center of the palm where no contact takes place.[7] This design was also noted in a bartender from shaking cocktails (nickel). In peeling an orange, a medium-sized ball, the distal surface of the palm as well as the web between the index finger and thumb are affected.

The "small ball" type is distinct from the aforementioned type. A rubber ball, the size of a lime, touches chiefly the base of the thumb and index and middle fingers, combined with the adjoining areas of the hand. The larger the ball, the farther does the pattern extend to the hypothenar area, diagonally across the hand. Many objects of similar size, of other than ball shape, such as a cigaret lighter, a pocket knife, a leather key case, an electric razor or a match box, produced lesions at the same site about the base of the first three fingers and the adjoining part of the palm (fig. 3).

3. Lesions of the Central Aspect of the Palm: Dermatitis localized on the central portion of the palm usually originates from an oblong object the end of which is in contact with this area. If this end is rounded, as in an old-fashioned gear shift (rubber) or the knob of a cane, no other part of the hand manifests lesions of dermatitis. The platen knob of a typewriter and the metal knob of a soap dispenser should be mentioned here. In the latter instance, the area is about the size of a cherry. Combinations of this pattern occur with that of the "finger grip type," as in dermatitis from a screw driver with a plastic handle, or in combination with the "bar type," from the handle of a pan or a vacuum cleaner. Lesions in this area furthermore suggest tooth paste, tooth powder or condiments or other powdered food substances which are used in cooking and which are placed in the palm of the hands.

B. Dermatitis on Volar and Dorsal Surfaces.—Because combinations of manifestations on volar and dorsal surfaces were commoner in our series than those on the dorsal surface alone, they form the second main division in our classification (fig. 4).

7. The lesions of the "large ball" type of dermatitis may resemble those of psoriasis of the hands.

1. Total Surface of the Hand: While practically any dermatitis on the hand may expand from the original focus to the total surface of the hand, there are two rather clearly recognizable designs of generalized dermatitis of the hands, namely, dermatitis from the dyes of gloves and dermatitis from soaps and washing powders. They can be distinguished from each other, since in "glove dermatitis" the border

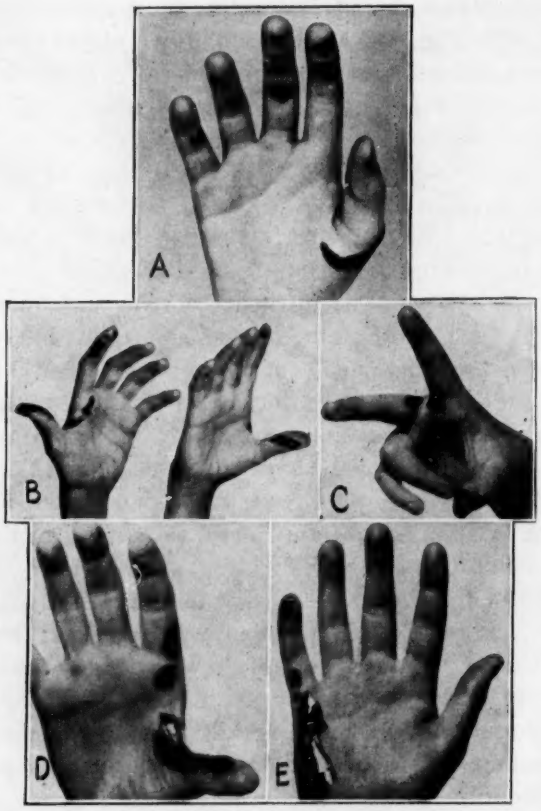

FIG. 4.—Contact dermatitis. *A*, pattern on the fingers only, resulting from contact with scissors. Other sources of similar pattern are fountain pens, pencils, cigarets, cigaret holders, pipes, finger cots, rings, bowling balls, hair curling (hair cosmetics), peanuts, popcorn, olives, dipping of fingers in fluids and thimbles. Interdigital lesions: *B*, due to knitting, and *C*, due to contact with a golf tee. Similar patterns are those from water faucets, from handling tin cans, the mouthpiece of a dictaphone or the heel of a shoe. Miscellaneous patterns: *D*, due to contact with a large medicine bottle, and *E*, due to contact with a flat surface. Sources of patterns are soap, gloves, plants, hypodermic medication, garments (dyes and fabric), golf glove clasps, bracelets and boxer's gloves.

is sharply defined on the wrist or the forearm and since the interdigital spaces as well as the center of the palm are not as intensively irritated in dermatitis due to gloves as in that from soap. Because the hands are usually covered up for some time by the gloves, the skin in this type of dermatitis tends to become easily infected.

In dermatitis due to soap, on the other hand, the lesions are not as symmetric as those of "glove dermatitis." From washing clothes, the predominant sites appear where the soap is held, namely, on the hypothenar region of the left hand. The interdigital spaces, where the soapy liquid tends to accumulate and which are often not thoroughly dried after washing, are also subject to greater irritation than other parts of the hand. These areas are prone to secondary infection. Any fluid, or semifluid, such as creams, lotions, hair tonics, juices from fruits or vegetables and solutions of various chemicals, as well as glove powder and insect powders, should be considered in differential diagnosis of such lesions. Of special importance here is the dermatitis encountered in dentists, physicians and veterinarians from drugs which are administered by hypodermic injection. While the whole hand may be involved, the points of greatest irritation are the finger tips.

2. Fingers: The whole surface of either a single finger or combinations of several may represent sites of dermatitis. If the distal part of a single finger is covered by such objects as a thimble or a rubber finger cot, dermatitis may arise on the respective area. Modifications of the "finger grip type" are encountered from reaching into a bowl for such foods as peanuts, popcorn or olives.[8] They affect the entire surface of the distal portion of the first three fingers completely instead of the volar surfaces alone. Dermatitis from a ring presents a bandlike lesion, localized where the ring is worn and extending onto the opposite finger. In a grocer, two well demarcated areas of dermatitis, covering the whole surface of the ring and little fingers, were due to dipping his fingers into a certain cleaning fluid. Dermatitis from a bowling ball affects the tips of the index and middle fingers and the thumb.

Favorite sites are the adjoining surfaces of index and middle fingers. The plastic of a pen, the varnish or wood of a pencil, the plastic or metal of a cigaret holder, cigarets themselves, the wood of a pipe and a certain button-like type of door knob, which is held between the two fingers, are objects which were encountered.

Among patterns affecting combinations of several fingers, those from scissors show rather typical circular bands around the thumb and the middle and ring fingers. In women, dermatitis localized on the index or middle finger, slightly involving the ring finger, is caused by hair-setting fluids or other hair cosmetics which are in contact with these parts when the hair is wound around the fingers for the purpose of curling it.

3. Interdigital Spaces: In all these contacts the web space between the fingers, especially between the index and middle fingers,

8. This was noted particularly in 2 patients who were simultaneously contact sensitive and atopically sensitive to these foods.

may or may not be involved. In two examples in which this area was practically the only one affected the disease was due to the dye or plastic of a golf tee and to the dye of knitting yarn.

The web space between the index finger and the thumb plays a part in the process of gripping many objects and has been dealt with under other headings, especially that of the "small ball type." In only a few instances was this area the exclusive site of the lesions, namely, in a patient who was contact sensitive to the oil of grapefruit rind and in another sensitive to the label of a tin can. Another person presented dermatitis in the same area from contact with spilled merthiolate which had been running down the medicine bottle. The mouthpiece of a dictaphone and the heel of a shoe (leather dye) are other sources of this type.

C. Dorsal Surfaces Only.—In lesions confined exclusively to the dorsal surface of the hand, we encountered difficulties in determining the causative agents. Only few showed a clearly defined pattern. In several patients with dermatitis about the central area of the dorsal surface, both inhalation of, and contact with, ragweed pollen were observed to be responsible. In others the condition was aggravated by their eating certain foods to which they were sensitive. Conversely, there are certain patterns of contact dermatitis on the wrists of patients with atopic eczema from contact with fabric or dyes of garments. Friction from these garments on the skin appears to be a contributing factor.

In a boiler operator, dermatitis of the dorsal parts of the fingers and the hand was due to his daily routine of touching the oily surface of the boiler to determine whether the boiler was getting warm. Other instances of dermatitis on the dorsal surface only were observed in an office stationery salesman, who was in the habit of reaching into a file of manila folders, to which contact sensitivity existed and in a grocer, due to sensitivity to nickel, who manifested a lesion on the dorsum of the hand from the clasp of a golf glove. In dermatitis from the oil of chrysanthemum leaves, the dominant lesions were located on the dorsal surfaces of the fingers and hands.

SUMMARY

In contact dermatitis of the hands a characteristic pattern of the lesion is often detectable. This design furnishes a clue to the cause of the lesion. Some of the factors influencing the design of the lesion are the power of the grip, the shape of the hand and the size and consistency of the object; the presence of secondary infection, secondary contact and atopic sensitization may alter this pattern. Based on these patterns, a preliminary classification of dermatitis of the hands is presented, which is suggested as the framework for future additions and modifications. Its purpose is to detect and catalog new causative agents.

10 Peterboro Avenue.

LOW AND HIGH TEMPERATURE COAL TARS IN THE TREATMENT OF ECZEMA AND PSORIASIS

A Clinical Investigation and Evaluation

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BOSTON

THE USE of "tar" as a panacea for cutaneous afflictions was described nearly two thousand years ago by Dioscorides.[1] It is true that it was not coal tar but "asphalt" that Dioscorides had in mind, for coal tar was not known at that time. The healing properties and usefulness of "asphalt" for preserving the beautifying qualities of the complexion are recorded by Samuel Foote.[2] The words "asphalt," "pitch," and "tar" were used loosely and often interchangeably until recent times. Coal tar was first discovered and described by Becher and Serle[3] in 1681. This substance was a natural successor of asphalt in the treatment of cutaneous diseases.

Today the word "tar" has a more restricted meaning than it formerly had. According to Abraham[4] the term is applied to pyrogenous condensates obtained by the destructive distillation of organic materials. He stated that it is dark in color and of liquid consistency, possesses characteristic odors, is slightly volatile at high temperatures and is composed principally of hydrocarbons, sometimes containing carbonaceous constituents which are for the most part soluble in carbon disulfide and which yield water-soluble sulfonation products. The terms "coal tar" and "coal tar pitch" include the tars and corresponding pitches recovered as by-products from bituminous coal in gas

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1. Dioscorides, cited by Abraham.[4]

2. Cited by Abraham,[4] p. 49.

3. Becher, J., and Serle, H.: British Patent No. 214, 1681.

4. Abraham, H.: Asphalts and Allied Substances: Their Occurrence, Modes of Production, Uses in the Arts and Methods of Testing, ed. 5, New York, D. Van Nostrand Company, Inc., 1945, vol. 1, p. 62.

works, coke ovens, blast furnaces and gas producers, as well as the tars produced by various low temperature processes.[4]

The process of refining coal tar by fractional distillation in closed retorts is essentially the same today as it was when first introduced by Haskins[5] in 1746. The process was described as "a new method for extracting a spirit of oil from tar, and from the same process obtaining a very good pitch."

Most of the coal tars produced in the United States are obtained from coke ovens equipped to recover by-products. The temperature of coking varies from 1,000 to 1,300 C. From 3.0 to 6.4 per cent of the coal is recovered as tar. These tars are known as high temperature coal tars. Low temperature coal tars are derived from the carbonization of coal at 400 to 700 C. They are of liquid consistency and contain a comparatively small quantity of carbon. They contain from 50 to 80 per cent hydrocarbons and from 20 to 50 per cent tar acids.

Schulz and Prunet[6] described a chracteristic test for low temperature coal tars. From 1 to 2 cc. of oily distillate is shaken with 5 cc. of an aqueous solution of ferric oxalate or ferric citrate. The aqueous layer becomes dark blue, which turns lemon yellow on acidifying with tenth-normal sulfuric acid. The blue tint reappears on neutralizing the acid with alkali. An excess of alkali changes the blue to purple and then to red. High temperature coal tars do not show these color changes.

Little is known about the chemical composition of the coal from which the coal tar is derived, for during the heating process many of the original components suffer decomposition. The simple hydrocarbons polymerize at high temperatures to give several substances of high molecular weight that were not present in the coal.

Abraham[7] pointed out that "the type of coal exerts a greater influence on the character of the tar than does the particular mode of treatment, and, in general, much variation occurs in the composition and character of the tars produced commercially." This is true; but it is also true that the character and composition of the tar depend on the temperature and mode of treatment of the coal in producing it.[8] The literature on coal tars does not state the difference in chemical composition between one type of coal tar and another. It also fails to indicate the difference of the chemical composition of coal tars produced from the same coal and at the same temperature but made

5. Haskins, H.: British Patent No. 619, 1746.

6. Schulz, F., and Prunet, J.: New Reactions of Low Temperature Tars, Bull. Soc. chim. **35**:638, 1934.

7. Abraham,[4] p. 381.

8. Abraham,[4] p. 384.

by different methods. Weiss and Downs[9] gave the chemical composition of a high temperature coke oven tar; this analysis, unfortunately, has been interpreted by many workers to be typical of all coal tars. Many of the synthetic coal tars that are being used in medicinal preparations are based on the Weiss and Downs formula.

The National Formulary VIII specifications for coal tar are not particularly selective, for they permit coal tar of all types to be used in medicine. The reason for this omission in selectivity in the monograph lies in the fact that no one has as yet shown that there is any difference in the therapeutic activity of the different tars that meet the specifications. We hope to show in this paper that there are differences in therapeutic activity in the different coal tars that meet the official specifications.

Some dermatologists have expressed the belief that the mode of compounding the coal tar determines its therapeutic effectiveness and others that the source of the coal tar or the temperature at which it was made is more important than the manner of compounding. But no one has determined experimentally, in the manner in which we have carried out this investigation, whether the low or the high temperature coal tars should be used.

White[10] expressed the belief that the manner of compounding coal tar is more important than the type of tar used. Downing, Ohmart and Di Cicco[11] have shown that the coal tar ointments containing zinc oxide, prepared by different methods, reveal no significant differences in their therapeutic effects, provided that the same type of coal tar is used throughout the experiment. Combes[12] pointed out that considerable variations in the action of coal tar may result from improper compounding; but he stated the belief, also, as did Downing and his co-workers, that the variation in the composition of coal tars is responsible for some of the variation in their therapeutic effectiveness. Furthermore, Combes stated that low temperature coal tars are to be preferred for medicinal purposes and that high temperature coal tars are undesirable medicinally. Our observations do not support this belief.

In the present investigation we prepared an ointment that had shown considerable promise in the treatment of eczema and psoriasis. This ointment was manufactured in large quantities from eight dif-

9. Weiss, J. M., and Downs, C. R.: Some of the Constituents of Coke-Oven Tar, J. Indust. & Engin. Chem. **15**:1022, 1923.

10. White, cited by Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940, p. 46.

11. Downing, J. G.; Ohmart, L. M., and Di Cicco, G.: Coal Tar in Dermatologic Preparation, Arch. Dermat. & Syph. **49**:421 (June) 1944.

12. Combes, F. C.: Coal Tar in Medicine, Indust. Med. **13**:500, 1944.

ferent coal tars. All eight of these samples met National Formulary specifications. The temperatures and the mode of preparing the coal tars were noted, and only the coal tars that could be obtained on repeat orders were used. The preparations made from these coal tars were largely used in cases of either eczema or psoriasis.

We have grouped under eczema all those cases in which there was vesiculation, weeping or crusted patches. Included under this

TABLE 1.—*Key to the Different Types of Coal Tar Used*

Sample No. or Letter	Suppliers Identification of Sample	Source of Supply
A	Kopper's crude coke oven tar	Everett, Mass.
B	Kopper's crude coke oven tar	Providence, R. I.
C	Kopper's crude horizontal retort tar	Pittsburgh
D	Kopper's crude vertical retort tar	Pittsburgh
EN	Neville refined coal tar	Neville Island, Pa. Pittsburgh

(These are all high temperature coal tars according to the supplier's claims. They all failed to give a positive Schulz-Prunet reaction.)

F	Pittsburgh Coal Carbonization Company	Pittsburgh
G	Midwest Radiant Corporation	St. Louis
H	Lehigh tar acid oil, a low temperature lignite coal tar	The Lehigh Briquetting Co., Dickinson, N. D.

(These three samples are low temperature coal tars. They all gave a positive Schultz-Prunet reaction.)

5	A well known commercial product prescribed for eczema and psoriasis	Company I
10	A well known commercial product prescribed for eczema and psoriasis	Company II

TABLE 2.—*Formula of the Coal Tar Ointment Used in This Investigation*

Corn starch, U.S.P.	25 Gm.
Zinc oxide, U.S.P.	15 Gm.
Solution of coal tar made according to the National Formulary and representing 2.66 Gm. of coal tar	13.3 cc.
Distilled water, U.S.P.	6.4 cc.
Wool fat, U.S.P.	6.25 Gm.
White petrolatum, U.S.P.	32.50 Gm.
Paraffin oil, U.S.P.	6.25 Gm.

classification are cases of atopic dermatitis, persistent contact or industrial, nummular, seborrheal and varicose eczema.

In addition to the eight different coal tars used in preparing these samples, two of the better known coal tar preparations prescribed in the Greater Boston area were also tested and compared with the others. Five of the coal tars used were high temperature and three

were low temperature types. Each sample of tar was used in turn in this formula.

More than 600 subjects were studied in this investigation over a three year period. First, a formula with sample A was used as a control, which was compared with B, C, D, EN, F, G, H, 5 and 10 in therapeutic effectiveness. Then sample B was used as the control, and it was compared with all the other tars. This process was carried on with all the tars. It soon became apparent that tar A produced the best results in eruptions accompanied with intense itching, vesiculation and oozing. Its antipruritic and desiccating properties were apparently superior to those of the other tars. In like manner it soon became apparent that tar D was superior to the other tars in squamous or scaly eruptions, such as are seen in psoriatic diseases. In some subjects as many as six different tars were used before it was decided that A or D was better than the other tars.

The great majority of subjects with cutaneous diseases that were treated with these ointments were benefited either by sample A or by sample D. Few untoward reactions occurred when sample A was used, and the cases in which coal tar therapy had to be discontinued were cases of atopic dermatitis or neurodermatitis. It is well known that at times patients with atopic dermatitis are intolerant of almost all types of local medication. Sample D elicited no untoward reactions in the cases in which it was of value, but when it was used for such diseases as varicose eruption it produced from 8 to 10 per cent of localized dermatitis.

Before these comparisons were instituted ointments containing all the tars were tried in patch tests on about 100 subjects with normal skin. It is interesting to note that if a patient was sensitive to any one coal tar ointment he was sensitive to all. However, clinical trial was deemed more valuable than patch tests; so these were discontinued.

Neither sample A nor sample D gave any untoward results when their use was followed by treatment with ultraviolet rays. In our hands, tar A and tar D were observed to be the most dependable tars.

The ointment prepared by the formula given is a smooth nongreasy ointment, grayish rather than the dirty black so frequently seen. It is easily removed, and yet, when applied even in small amounts, as on the scalp, it forms a film that adheres well and lends itself successfully to treatment with ultraviolet rays.

Coal tar should not be used when the skin is extremely tender or shows pinpoint pustulation.

It will be observed that sample A and sample D are both high temperature coal tars and that these tars were effective against the majority of the cutaneous diseases treated.

It will be further observed that no single coal tar is the best type for all purposes. However, sample A was better than any other sample used in the treatment of vesicular eruptions, and sample D was better than any other sample in the treatment of squamous diseases.

It will also be observed that the ointment base is not the water-soluble base so frequently employed. Our base was used because it was observed to be ideally suited for these preparations and because it lends itself successfully to supplementary treatment with ultraviolet rays.

CONCLUSIONS

The ointments herein described are not wonder ointments. They are merely offered as an improved formula for an old medicament. When indicated, they were observed to be superior to the other tars tested in this investigative work. Tar is a useful drug in dermatologic conditions, but it must be chosen with care and used in subacute and chronic conditions. It should never be used in the acute stage of dermatitis due to an external irritant or a constitutional cutaneous disease, such as psoriasis. When indicated, it is merely an adjunct to other treatment, both local and general.

IN VITRO STUDIES OF MICROSPORON AUDOUINI INFECTION OF THE HAIR

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IN RECENT years the attention of physicians in the United States, particularly in the eastern half of the country, has been focused on an epidemic of ringworm of the scalp in school children. The reports indicate that the organism responsible for the disease in the majority of the cases has been Microsporon audouini. In 1822 Wilkinson[1] reported an epidemic in England, and in 1843 Gruby[2] discovered one of the causative organisms, which he named Audouini. In 1894 Sabouraud[3] succeeded in growing this organism in pure culture on artificial mediums. In 1925 Margarot and Deveze[4] described the use of Wood's light as an aid in the diagnosis of tinea capitis. The interest in fungous disease antedates these discoveries by many centuries. Horsfall[5] stated that Homer, in 1000 B.C., mentioned the use of sulfur in the treatment of fungous disease and in 100 A.D. a Greek physician, Dioscorides, described the use of sulfur ointment as a therapeutic measure.

In the five years, 1937 to 1942, inclusive, only 60 patients with tinea capitis were treated in the University of Maryland department of dermatology, but from May 1943 through October 1946, 303 patients were under observation.

Davis,[6] of the Baltimore City Health Department Communicable Disease Division, stated that 362 cases were reported from within

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1. Wilkinson, J. H.: Remarks on Cutaneous Diseases, London, J. & A. Churchhill, 1822, p. 38.

2. Gruby, M.: Recherches sur la nature, le siege et le development du porrigo decalvans ou hytoalopecie, Compt. rend. Acad.d.sc. **17**:301, 1843.

3. Sabouraud, R.: Sur une mycose innominee de l'homme, la teigne tondante speciale de Gruby, Microsporum Audouini, Ann. Inst. Pasteur **8**:83, 1894.

4. Margarot, J., and Deveze, P.: Aspect de quelques dermatoses en lumiere ultraparaviolette: Note preliminaire, Bull. Soc. d. sc. méd. et biol. de Montpellier **6**:375, 1925.

5. Horsfall, J. G.: Fungicides and Their Action, Waltham, Mass., Chronica Botanica Co., 1945.

6. Davis, W.: Personal communication to the author.

the city in the months of January and February of 1947. A noteworthy epidemic was reported by Schwartz and his co-workers[7] in Hagerstown, Md., in 1944. Reports from New York by Mitchell and his associates,[8] and from Minneapolis and St. Paul by Steves and Lynch[9] indicated the presence of large numbers of cases in those cities. Recently outbreaks have also been reported in Philadelphia, Niagara Falls, N. Y., Detroit and Chicago.

The presence of an epidemic acts as a stimulus to medical investigators to attempt to produce new methods of treatment to eradicate the offending disease, and this one has not proved an exception. The M. audouini infection of the scalp, which is the predominant type in this epidemic, has been observed to be extremely resistant to most chemotherapeutic measures. Sutton and Sutton[10] gave a complete résumé of the various recommended drugs up to 1940, together with a complete bibliography of the various investigators sponsoring them. Schwartz and his co-workers[7] used 5 per cent salicylanilide in a "carbowax" base and a saturated solution of copper undecylenate in a "carbowax" base in the treatment of patients in Hagerstown and stated that 98 per cent of the patients who gave satisfactory cooperation were cured. Livingood and Pillsbury[11] used two preparations of tincture of iodine (one of which contained a wetting agent), iodine ointment, phenyl mercuric nitrate, ammoniated mercury, sulfur and salicylic acid. They concluded that these drugs were of little or no value in the treatment of tinea capitis. Thus far, most dermatologists agree that roentgen ray epilation, first described by Sabouraud and Noire,[12] is the most satisfactory means of treatment. Roentgen therapy does not kill the fungus or its spores, but simply acts as an epilating agent, so that the hair falls out. Infected hair removed by roentgen rays produce an active growth when planted on Sabouraud's mediums. Thallium acetate also acts as an epilating agent, but its dangerous toxic effects overblance its value as a therapeutic agent.

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7. Schwartz, L.; Peck, S. M.; Botvinick, S.; Leibovity, A. L., and Frasier, E. S.: Control of Ringworm of the Scalp Among School Children, Public Health Bulletin 294, Federal Security Agency, United States Public Health Service, 1946.

8. Mitchell, H. H.; Story, L. S., and MacDonald, J. C.: An Epidemic of Ringworm of the Scalp, Pub. Health Nursing **35**:564, 1943.

9. Steves, R. J., and Lynch, F. W.: Ringworm of the Scalp, J.A.M.A. **133**:306 (Feb. 1) 1947.

10. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939.

11. Livingood, C. L., and Pillsbury, D. M.: Ringworm of the Scalp, J. Invest. Dermat. **4**:43, 1941.

12. Sabouraud, R., and Noire, H.: Traitement des teignes tondantes par les rayons X a l'Ecole Lailler (Hospital St. Louis), Presse méd. **2**:825, 1904.

It is the purpose of this investigation to demonstrate the resistance in vitro of M. audouini infection of the hair to the action of the so-called fungicides as well as to some other substances. The infected material used in this study was obtained from patients seen in the department of dermatology of the University of Maryland and the author's private practice. The patients were examined under the Wood light, and the infected hair was removed manually by epilating forceps, placed in sterile test tubes, labeled and placed aside for study. Each lot was cultured on stock Sabouraud's medium in the dark room, using the Wood light to insure that only fluorescent hairs were planted. Each experiment was conducted in the same fashion, and a control tube was planted each time a study was instituted.

REPORT OF EXPERIMENT

EXPERIMENT 1.—Ten cubic centimeters of water were added to a tube containing a tuft of fluorescent hair from which a culture of M. audouini had previously been grown. This tube was heated over a Bunsen burner until the mixture of hair and water had boiled for five minutes. More water was added from time to time to keep the amount of fluid constant. The tube was periodically examined under the Wood light, and it was noticed that the fluorescence gradually left the hair and was assumed by the water. At the end of five minutes none of the hairs responded to the filtered ultraviolet rays. They were then inoculatd on Sabouraud's mediums and observed periodically for twenty-one days. No growth was obtained. The results of this experiment are similar to those obtained by Davidson and Gregory, [13] who concluded that the fluorescence was due to some change in the hair substance following the invasion of the hair by the fungus.

EXPERIMENT 2.—In order to demonstrate the longevity of the spores of M. audouini in hair, on Jan. 3, 1947, a large tuft of fluorescent hair was placed in a sterile test tube which was fitted with a rubber stopper. At weekly intervals a small portion of hair was removed and planted on Sabouraud's medium, and positive cultures were obtained with each planting. On May 8, after one hundred and twenty-five days, these hairs were proved to be still infected with the spores of M. audouini by the use of the Wood light and culture mediums. The results of this experiment substantiate those obtained by Farley,[14] who demonstrated that hairs infected with fungi produced a growth on culture mediums even after four hundred and twenty days.

EXPERIMENT 3.—Experiments 3 and 4 were performed to demonstrate the resistance of M. audouini to a variety of chemical substances which have been used in the treatment of patients infected with this fungus. Tufts of infected hair were placed in each of three sterile test tubes and were treated in the following manner: (*a*) To tube 1 was added 3 per cent tincture of iodine; (*b*) to tube 2 was added tincture of merthiolate in dilution of 1 to 1,000, and (*c*) to tube 3 was added Castellani's carbolfuchsin mixture.

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13. Davidson, A. M., and Gregory, P. H.: Note on Investigations into Fluorescence of Hairs Infected by Certain Fungi, Canad. J. Research **7**:378, 1932.

14. Farley, D. L.: Viability of Ringworm Fungi in Dry Cutaneous Material, Arch. Dermat. & Syph. **3**:759 (June) 1921.

The tubes were then fitted with rubber stoppers and allowed to stand for five minutes, following which the hairs were removed and allowed to dry on filter paper. They were then inoculated on tubes of Sabouraud's medium, and a control tube was also planted. The first filaments of growth were noticed on the control tube after four days, and after fourteen days the entire slant was covered with a luxuriant growth of M. audouini. The hairs treated with Castellani's mixture and those treated with tincture of merthiolate produced their first growth in six to eight days, respectively, and after eighteen and sixteen days, respectively, the growths had completely covered the culture mediums. No growth was noticed on the medium in the tube containing the hairs treated with tincture of iodine after twenty-one days of observation.

EXPERIMENT 4.—A tuft of infected hair was inserted into each of a series of twelve sterile test tubes, each of which was fitted with a rubber stopper. One of these was placed aside as a control, and into each of the others was placed 5 cc. of one of the medicaments mentioned in table 2. The liquids were poured into the tubes, so that all of the hairs in the respective tubes were covered. Ointment containers were each filled with one of the six ointments mentioned in table 2 and a tuft of infected hair was thoroughly mixed into each one. These preparations were placed aside for five days. The liquid preparations were observed daily under the Wood light to denote any diminution in fluorescence of the hair under

TABLE 1.—*Data on Experiment 3*

Cultures	No. of Days After Planting for Initial Growth to Begin	No. of Days After Planting for Culture to Obtain Full Growth
Control culture; hairs not treated	First filaments noted in 4 days	Full growth on slant in 14 days
Tincture of iodine (3%) treated hairs	No growth	No growth after 21 days
Castellani's mixture treated hairs	First filaments noted in 6 days	Full growth on slant in 18 days
Tincture of merthiolate (1 to 1,000) treated hairs	First filaments noted in 8 days	Full growth on slant in 16 days

treatment. The only tubes to show any change were those containing phenol and ether. The hairs in the phenol tube began to lose their fluorescence at the end of the second day, and in five days there was no reaction when they were exposed to the Wood light. The ether became slightly fluorescent in twenty-four hours, but there was no apparent change in the reaction of the hair even at the end of five days. Each tube was then opened, and the hairs were removed and washed in water, alcohol and ether and allowed to dry on filter paper before being planted on Sabouraud's medium. The results are recorded in table 2. The ointments were melted over a gentle flame, and the hairs were removed and washed in water, alcohol and ether before planting. These results are also recorded in table 2.

EXPERIMENT 5.—It was the purpose in this experiment to demonstrate the inhibiting effect of some of the more commonly used fungicides when mixed with Sabouraud's medium on the growth of M. audouini. The medium used was freshly prepared by the biologic laboratory of the university hospital. It was remelted over a water bath, and the preparations mentioned in table 3 were added in concentrations of 1 per cent and 5 per cent by volume. In order to get the ointment preparations to remain thoroughly mixed with the mediums, it

TABLE 2.—*Data on Experiment 4*

Medicaments used in Treating Hair	No. of Days After Planting for First Filaments of Growth to Appear on Mediums	No. of Days After Planting for Growth to Cover Slant of Sabouraud's Medium
Control; no medicament applied to hairs	4	14
Propylene glycol dipropionate	4	14
Propylene glycol dipelargonate	4	14
"Cresatin" solution	5	16
Phenol 90%		No growth after 21 days
Formaldehyde solution 5%	7	19
Xylene	4	14
Trimethyl cetyl ammonium pentachlorphenate solution 3.2%	8	18
Alcohol 90%	6	16
Acetone	4	14
Ether	4	14
Proprietary fungicide containing thymol	6	16
Trimethyl cetyl ammonium pentachlorphenate ointment 2.2%	10	17
Ammoniated mercury ointment 5%	10	19
"Desenex" ointment 5%	10	19
Sulfur ointment 5%	10	19
Sodium proprionate ointment 20%	10	19
5% Salicylanilide in "carbowax"	10	19

TABLE 3.—*Data on Experiment 5, Demonstrating the Effect of Different Concentrations of Medicaments When Mixed in Sabouraud's Medium on the Growth of Microsporon Audouini from Infected Hair*

Preparation Used	Concentration of Active Ingredients in the Preparation Used (Percentage)	Growth Observed When Sabouraud's Medium Contained 1 Per Cent of Preparation	Growth Observed When Sabouraud's Medium Contained 5 Per Cent of Preparation
"Cresatin" solution	80	yes	no
Phenol	90	no	no
Tincture of merthiolate	0.1	no	no
Merthiolate solution	0.1	yes	no
Propylene glycol diproprionate	100	yes	yes
Propylene glycol dipelargonate	100	yes	no
Zinc undecylenate undecylenic acid ointment	20 5	yes	no
Sodium proprionate ointment	20	yes	no
Castellani's mixture		no	no
Tincture of iodine	3	no	no
Trimethyl cetyl ammonium pentachlorphenate	1	yes	no

was necessary to agitate the mixture from time to time as it cooled. The final preparation, as it solidified into a slant, was homogenous. As previously stated, the preparations were added in concentrations of 1 per cent and 5 per cent; however, the percentage of the active ingredient in the finished preparation was much smaller than this because of the various concentrations of the drugs in their respective formulas.

The prepared tubes were each inoculated with tufts of infected hairs, specimens of which had previously been cultured on untreated mediums and from which growths of M. audouini had been obtained. These slants were observed at daily intervals, and an inoculation was not deemed a failure unless a growth had not been obtained after twenty-one days. At the end of this period of observation hairs were removed from the surfaces of the slants containing the 5 per cent mixtures and were washed in water, alcohol and ether. After this preparation they were then reinoculated on untreated mediums. Prior to planting it was observed that hairs from all the tubes except the ones removed from the phenol slants had retained their fluorescence. All slants except those containing the hairs treated with phenol showed beginning growth after six days and full growth after twelve days.

SUMMARY

It is evident from the results of these experiments that the term fungicide should not be loosely applied to any drug which is to be used in treating ringworm of the scalp when the offending organism is Microsporon audouini. That these drugs are for the most part fungistatic, at least in vitro, has been demonstrated. M. audouini has great longevity, as demonstrated by its ability to live in the stage of sporulation without oxygen for one hundred and twenty-five days. The spores are killed by prolonged boiling in water, as demonstrated by the inability to produce a growth from hairs which had been boiled for five minutes.

The third experiment demonstrated the inefficacy of tincture of merthiolate in dilution of 1 to 1,000 and of Castellani's mixture to inactivate the spores of M. audouini, but showed that 3 per cent tincture of iodine prevents these infected hairs from producing a growth on mediums.

In the fourth experiment it was demonstrated that the only preparation used which inactivated the spores and prevented them from producing a growth was 90 per cent phenol. Some of these medicaments, especially the ointment preparations, definitely retarded the appearance of a growth, but filaments had appeared on all tubes at the end of ten days, regardless of the drug used. These in vitro experiments indicate that none of the more recently discovered so-called fungicides studied in these experiments have any greater fungicidal power than preparations which have been in use for many years.

In the fifth experiment an attempt was made to demonstrate the inhibiting effect that certain drugs have on the growth of M. audouini

when these preparations are mixed with Sabouraud's medium. Thus, it is shown that tincture of iodine, tincture of merthiolate, phenol and Castellani's mixture definitely prevent the growth of the fungus, but the spores remain active, and when the hairs are recovered and replanted on untreated mediums, growths are obtained, as was demonstrated in every case except when the hairs were recovered from mediums treated with phenol.

CONCLUSION

1. As demonstrated by in vitro experiments, the term fungicide may be a misnomer when applied to the drugs now in use in the treatment of Microsporon audouini infection of the hair. This is true of all drugs used in these experiments except tincture of iodine and 90 per cent phenol. The term fungistatic is suggested as being more appropriate, unless the fungicidal properties of the drug have been actively demonstrated both in vitro and in vivo.

2. The spores of M. audouini are capable of existing in a resting state for at least one hundred and twenty-five days, still maintaining the ability to produce active infection, as demonstrated by the ability to produce a growth on artificial mediums.

3. The results of these experiments indicate that sodium proprionate, salicylanilide, propylene glycol diproprionate, propylene glycol dipelargonate, zinc undecylenate and undecylenic acid ("desenex"),[11] "cresatin metacresylacetate (Sulzberger)"[11] (acetic acid ester of metacresol) solution and ointment, tincture of merthiolate and trimethyl cetyl ammonium pentachlorphenate solution and ointment, at least in vitro, are no more actively fungicidal than tincture of iodine and ammoniated mercury ointment.

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PRURIGO OF HEBRA

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FERDINAND von Hebra, head of the Viennese school of dermatology in the nineteenth century, individualized and described in detail a clinical entity frequently observed in Central Europe at that time. This entity was of intense pruritus and characteristic papules, with a peculiar distribution, that appeared early in youth and lasted generally throughout life. This dermatosis, included in types of prurigo (pruritus and papules), was well studied and further commented on by Hebra's successor in Vienna, Kaposi,[1] and by French authors, Besnier and Doyon[2] (Kaposi's translators and commentators), Vidal,[3] Brocq[4] and Jacquet.[5] Since then, by Besnier's express suggestion, this disease has been called prurigo of Hebra.

We have had the opportunity of studying a case of prurigo of Hebra in a white native Argentine and of following up another case, of Viennese origin in a youth 18 years old, studied by Noussitou and Cordero.[6] We have reviewed the German, French and American literature on the subject and consider useful the identification of the principal causative histologic and pathogenic facts about prurigo of Hebra, about which there is considerable confusion.

CLINICAL SYMPTOMS

The dermatosis described by Hebra generally begins during the second year of life by an eruption of wheals or by strophulus, which

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1. Kaposi, M.: Pathologie et traitement des maladies de la peau, translated by E. Besnier and A. Doyon, Paris, G. Masson, 1891, vol. 1, p. 719.

2. Besnier, E., and Doyon, A.: Notes and Additions on the French translation of Kaposi.1

3. Vidal, E.: (*a*) Du lichen (lichen, prurigo, strophulus), Ann. de dermat. et syph. **7**:133, 1886; (*b*) Considerations sur le prurigo de Hebra, ibid. **3**:981, 1892.

4. Brocq, L.: Cliniques dermatologiques, Paris, Masson & Cie, 1927, p. 339.

5. Jacquet, L.: La pratique dermatologique, Paris, Masson & Cie, 1902, vol. 4, p. 58.

6. Noussitou, F. M., and Cordero, A., in Proceedings of the Asociación argentina de dermatologia y sifilologia, Nov. 13, 1946; personal communication to the authors.

does not differ from the ordinary lesions. They appear at irregular intervals and disappear without trace, until one recurrence is followed by the appearance of itchy papules which persist for some time. After each eruption these papules become more numerous, until the surface of the skin is covered with the elementary lesions, which will be described.

The lesions are small hard dry papules, 2 to 5 mm. in diameter and deeply embedded in the dermis. As they are elevated slightly above the surface and because they are of the same color as the skin, they are easier to palpate than to see.

These elementary lesions occur in groups of three or four papules; they do not become confluent, and they last for hours or days if they are not modified by scratching. Since scratching generally occurs, because prurigo of Hebra is intensely itchy, the papules that are subjected to scratching become covered by a black hemorrhagic crust; they then appear embedded in a red tumefield base. When the lesions heal, they frequently leave a permanent scar.

As a result of constant scratching, the skin becomes lichenified, especially on the knees and elbows, where the skin forms horny folds, making identification of the primary papules difficult.

The distribution of the papules and lichenified zones is pathognomonic of this dermatosis. The scalp is always free (Hebra, in Kaposi[1]); the face is scarcely involved; the chest is more involved than the face, the arms yet more and the legs much more than the arms, especially on the distal portions. The flexor surfaces of the limbs are always less attacked. The folds, popliteal spaces, palms and soles are almost always free of elementary lesions (papules).

Enlarged glands, sometimes the size of a fist, are frequently seen in prurigo of Hebra. They are the consequence of secondary impetigo and eczema, the commonest complications of this dermatosis.

Lichenification is different than that ordinarily seen in other dermatoses. In prurigo of Hebra there is no accentuation of the normal furrows, or quadrille, of the skin. The color is characteristic, being grayish brown. The skin is greatly thickened, tense and rough, and it forms a rigid shell where hairs, worn by constant scratching, grow sparsely and in brushlike fashion.

CLINICAL TYPES

Hebra classified variations of this dermatosis into two separate types: prurigo ferox, or agria, and prurigo mitis, according to the severity of the eruption, the degree of itching, the effects on general health and the existence of lesions on the face and elsewhere. Prurigo ferox of Hebra is generally considered incurable (referred to subsequently in this paper).

EVOLUTION AND PROGNOSIS

Most authors on the subject have expressed the belief that prurigo of Hebra can be cured only in childhood with constant care and medical attention, when the disease may be considered as being of the mitis type, Prurigo ferox, or agria, of Hebra is considered incurable (Hebra) as it can be cured only in rare circumstances. However, proper medical measures may achieve good results (Ehlers,[7] Besnier and Doyon,[2] Noussitou and Cordero[6] and others). French authors in general (Besnier and Doyon,[2] Jacquet[5] and Civatte[8]) and Danish authors (Haslund and Ehlers[9]) are not so pessimistic and have expressed the belief that the disease can be alleviated with the onset of puberty and with the passage of time. It is to be noted that the disease in the French cases was not so severe as in those described originally by Hebra and the Viennese authors. In any case, left to itself, without proper medical attention, prurigo of Hebra is a serious disease that exerts extensive influence on the physical and moral development of those affected. Because of insomnia and pruritus, which brings torture night and day, persons affected by prurigo of Hebra are pale and thin, lacking physical resistance and mental development, are untutored and sometimes aggressive, have questionable physical stability and are useless to society and a handicap to their families.

INCIDENCE AND CORRECTIVE FACTORS

Age of Onset.—Prurigo of Hebra begins in early childhood, between the ages of 2 and 5 years. Appearance of the disease at the end of the first year of life has been reported (Kaposi and Civatte[8b]). Cases of prurigo of Hebra are known to begin at 60 years or later in life (Spiethoff,[10] Ehlers,[9] Vidal,[3] Kaposi,[1] Besnier and Doyon[2] and Kanee[11]).

Sex.—Prurigo of Hebra appears to occur twice as frequently in male as in female subjects (Kaposi,[1] Civatte,[8b] Ehlers[7] and Hudelo[12]).

Race.—Jews seem to be more affected than non-Jews. The disease

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7. Ehlers, E.: Communication provisoire concernant une serie de recherches cliniques sur le prurigo de Hebra, Ann. de dermat. et syph. **3**:861, 1892.

8. Civatte, A.: (*a*) Prurits et grattage, Ann. de dermat. et syph. **7**:142, 1926. (*b*) Formes cliniques et pathogenie des prurigos, in Congres des dermatologistes et syphiligraphes de langue française, Paris, Masson & Cie, 1929, p. 143.

9. Ehlers,[7] in discussion on Civatte;[8b] Discussion et communications diverses, in Congress des dermatologistes et syphiligraphes de langue française, Paris, Masson & Cie, 1929, p. 128.

10. Spiethoff, B.: Prurigo Hebrae bei einem sechzig jahrigen Manne, Zentralbl. f. Haut-u. Geschlechtskr. **18**:151, 1925.

11. Kanee, B.: Prurigo of Hebra Ferox, Arch. Dermat. & Syph. **50**:113 (Aug.) 1944.

12. Hudelo, L.: Prurits et prurigos, Paris, Gaston Doin & Cie, 1932.

has been frequently reported in Central and Eastern Europe (Germany, Austria and Poland).

Environmental Factors.—Poverty, dietary deficiency and lack of personal hygiene are important environmental factors.

Jadassohn[13] reported notable improvement in his patients when they remained in the hospital for long intervals and recurrences when they returned to their homes. Occurrence of the disease in wealthy persons has rarely been reported. In Denmark, Ehlers[9] demonstrated the same facts by collective experience and inquiry. The incidence of prurigo of Hebra was frequent in Copenhagen in the second half of the nineteenth century and diminished in the twentieth century, following social and hygenic advances. The experience of Barber,[14] in England, paralleled Jadassohn's experience.

In Argentina, Sommer's[15] observations agreed with Ehlers'.[9] In the first twenty years of this century, many cases were reported. During the last twenty-five years cases have not totaled more than 5 (Guerrero,[16] Baliña,[17] Noussitou and Cordero[6] and our present case).

Heredity.—Kaposi,[1] Besnier[2] and Ehlers[7] noted the existence of familial trends in prurigo agria. Predominant familial occurrence was acknowledged by Kaposi,[1] Besnier and Doyon,[2] Ehlers[7] and Lutz.[18] Bompert (cited by Kanee[11]) told of the occurrence of prurigo of Hebra in five generations in a single family.

Frequency.—The infrequent occurrence of the disease and the difficulty of diagnosis by practitioners and even dermatologists, who tend not to think of prurigo of Hebra when diagnosis is made, may explain why so few cases have been reported. At all events, the disease is rare in America. Only a few cases have been reported in Chile (Chana[19]), Brazil (Castro[20a,b]) and Mexico (Arias[20c]). In the United States we have collected only 49 cases since Wiggleworth submitted his report in 1873 (Kanee[11]).

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13. Jadassohn, J., cited by Civatte.[8b]

14. Barber, H. W.: Studies of Allergy, Lancet **1**:1009, 1928.

15. Sommer, B.: Rev. argent. dermatosif. **1**:4, 1908; **4**:117, 1912; **6**:236 and 243, 1914.

16. Guerrero, M.: Arch. latino-am. pediat. **116**:284, 1922.

17. Baliña, P. L.: VII. Prurigos liquenes, neurodermitis, Rev. argent. dermatosif. **16**:630, 1932; Dermopatias y faneropatias, ibid. **17**:157, 1933; Dermopatias y faneropatia, ibid. **18**:141, 1934; Dermopatias y faneropatias diversas, ibid. **19**:278, 1935; Dermopatias y faneropatias diversas, ibid. **20**:359, 1936.

18. Lutz, W.: Discussions et communications diverses, in Congres des dermatologistes et syphiligraphes de langue française, Paris, Masson & Cie, 1929, p. 118.

19. Chana, P.: Algunas consideraciones sobre la etiopatogenia de los prurigos cronicos, Rev. argent. dermatosif. **24**:534, 1940

20. (*a*) de Castro, C.: Lichen urticatus e prurigo de hebra, Brasil. med. **57**:303, 1943; (*b*) O prurigo de Hebra em Minas Geraes, ibid. **57**:401, 1943. (*c*) Arias, O.: Personal communication to the authors.

Seasonal Influence.—Kaposi[1] and Ehlers[7] have referred extensively to seasonal influence in prurigo of Hebra. In general, the patients improve in summer and get worse in winter, but apparently the reverse may also be the case.

Alternance with Other Diseases.—Association of prurigo of Hebra with asthma (Beagoe, cited by Sutton and Sutton[21]) has been reported. Urticaria and strophulus have also repeatedly been mentioned. These last are, in fact, intimately related to prurigo of Hebra by their pathogenesis.

Other Possible Causative Factors.—Blood dyscrasias, glandular dysfunction and chronic infections, such as syphilis and tuberculosis, have frequently been incriminated. However, these factors appear to have only circumstantial influence.

Comment.—The enumeration of causative and pathogenic factors allows prurigo of Hebra to be considered an atopic dermatosis.

HISTOLOGIC ASPECTS

The first histologic descriptions of prurigo of Hebra show a peculiar confusion and differences of criteria. Articles by Leloir and Tavernier,[22] Darier,[23] Winkler,[24] Gans[65] and others have been commented on by Civatte.[8] This French author has made histologic studies on biopsy specimens of different evolutive phases of the typical eruptive elements of prurigo of Hebra, from the appearance of the papule of strophulus or the wheal of urticaria, which marks the first stages, to the final characteristic papule and peculiar lichenification. Lesions produced by scratching were also described.[8a] Civatte proved that papules of prurigo of Hebra present a different configuration according to the evolutive age of the lesions considered and the effect of scratching.[8]

According to Civatte the "initial lesion" is a cellular infiltration of the dermis formed by the polymorphonuclear neutrophils and leukocytes. In this infilatrate two zones can be distinguished: (*a*) a central zone, formed by an infiltrate of neutrophils that rapidly de-

21. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

22. Leloir, A., and Tavernier, A.: Note sur l'anatomie pathologique et la nature de la lesion elementaire de l'affection designee sous le nom de prurigo de Hebra, Ann. de dermat. et syph. **10**:613, 1889.

23. Darier, J.: Precis de dermatologie, ed. 4, Paris, Masson & Cie, 1928.

24. Winkler, M.: Prurigo, strophulus, pruritus, in Jadassohn, J.: Handbuch der Haut - und Geschlechskrankheiten, Berlin, Julius Springer, 1927, vol. 6, pt. 1, p. 301.

25. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1.

generate (leukolysis) and disappear in the center, and (*b*) a peripheral zone forming a halo of intact neutrophils.

The characteristic initial lesion of prurigo of Hebra is this neutrophil nodule with central leukolysis, which is similar to the early lesions of erythema multiforme (Civatte[8b]). This infiltrate forms small masses, with perivascular disposition in the papillary body and the corium.

The epidermal lesions that are seen in prurigo of Hebra are of secondary nature and according to Civatte[8a] are due to scratching.

Fig. 1.—*A*, prurigo of Hebra. The extensor surfaces of the limbs are covered with typical papules firmly embedded in the skin. *B*, typical papules on the buttocks and thighs.

The epidermis is hyperacanthotic. Sometimes, small cavities deeply set in necrotic stratum mucosum (prickle cells) can be seen, with moderate enlargement. These lesions were first described by Leloir and Tavernier.[22] Civatte[8a] proved that they were due to the mechanical effect of scratching on lichenified skin and that they were not pathognomonic of prurigo of Hebra. They may be seen in ordinary lichenification. In more advanced stages of the eruption the

histologic appearance is different. The infiltration loses its peculiar appearance (central and peripheral zones), forming a more homogenous infiltrate. Neutrophils are gradually replaced by the cells of chronic processes, such as histiocytes and lymphocytes.

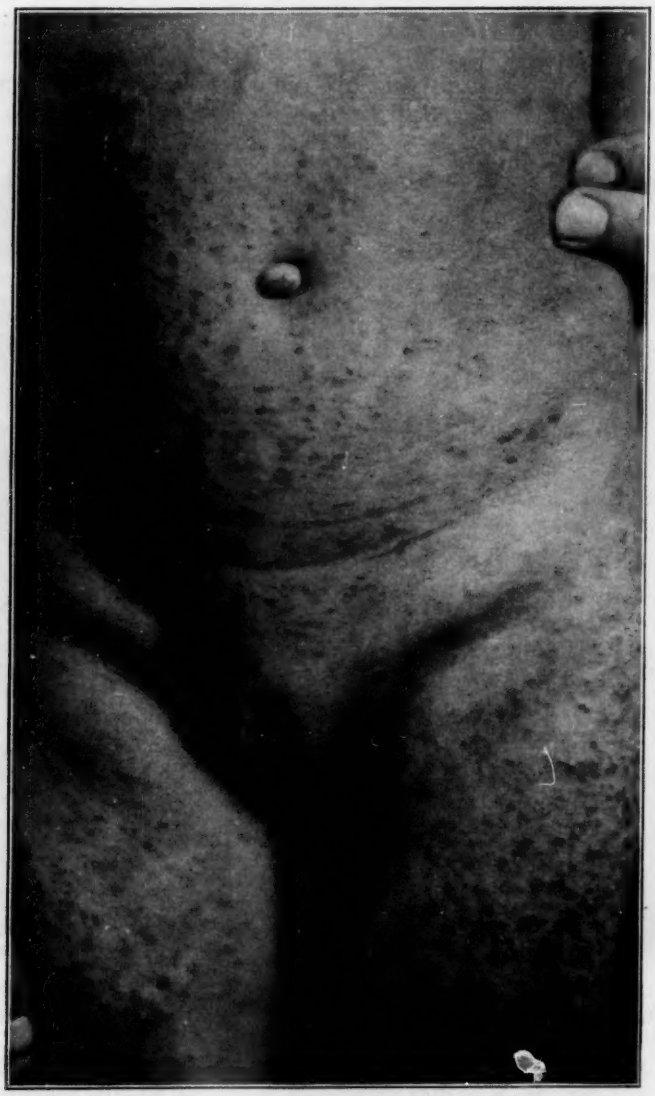

Fig. 2.—Prurigo of Hebra, showing enlargement of the inguinal glands.

REPORT OF A CASE

M. P., an Argentine white 6 year old girl, presented chronic dermatosis, which began four years prior to examination. The extensor surfaces of the limbs (fig. 1*A*), the back and the buttocks (fig. 1*B*) were covered with small hard shiny

horny papules, firmly embedded in the skin. The flexor surfaces of the limbs were less extensively attacked. The face, skull, palms, soles and folds were almost free of the eruption. The skin in general was lichenified and formed great horny folds on the knees (fig. 1*A*) and elbows. The enlargement of the axillary and inguinal glands is visible in figures 1*A* and 2.

The patient was in poor condition; she was pale and anemic; her weight was under normal, and she had been repeatedly treated for scabies.

The cutaneous appearance has been described previously in the text.

In clinical examination the pulmonary and cardiovascular apparatus was observed to be normal, and in the abdominal cavity the only abnormalty was the slight increase in size and the consistency of the liver.

Roentgenograms of the thorax did not show any abnormality. Reactions to tuberculin tests (Mantoux), with old tuberculin (Koch) in dilution of 1:1,000, were slightly positive.

Cutaneous Tests.—Intradermal and scratch tests with different allergens were made. Mildly positive reactions were obtained with wool and silk. A strongly positive reaction was obtained with house dust.

Examination of the Blood.—The red blood cell count was 3,130,000 per cubic millimeter, the white blood cell count 6,800 per cubic millimeter and the hemoglobin (Sahli) 11.5 Gm. The differential count showed eosinophils to be 4 per cent. Reactions to Wassermann, Kahn standard and presumptive tests were all negative. Cholesterol was 1.65 Gm. per hundred cubic centimeters.

Uranalysis.—Normal figures were recorded for the urine except that the content of indican was above normal.

Examination of the Feces.—The feces showed eggs of Oxyuris vermicularis.

Histologic Study.—Biopsies were made during different stages of the disease and of different sites. Paraffin and frozen sections were employed, stained with hematoxylin and eosin, and Van Giesson, Pinkus (orcein-Giemsa) and argentic impregnations (silver carbonate of Rio Hortega).

The first biopsy was made of a recent papule on the back, similar to that of strophulus, twenty-four hours after its appearance. Histologic study of this lesion showed clearly the neutrophil nodes and central leukolysis (fig. 3) described by Civatte[8] and the perivascular disposition of other infiltrations in the papillary body and reticular part of the dermis. In figure 3 it can be seen that the central part of the node was necrobiotic, with visible alterations of the collagenous fibers. According to our knowledge this fact has not been expressed by other authors.

The second biopsy was of a papule more than a week old, taken from a buttock (fig. 4). In figure 4 one can notice the gradual replacement of the neutrophils by lymphocytes, histiocytes and fibroblasts, with perivascular and perinodular distribution. The blood vessels showed moderate congestion.

The third biopsy was of a lichenified zone of the anterior aspect of the thigh. In figure 5 one can see epidermodermic changes. In the papillary aspect of the dermis and in the corium can be seen the infiltrates and their perivascular distribution, just as in figure 4. The epidermis was acanthotic, with scales and crusts. In some fields we were able to see the cysts of Leloir and Tavernier,[22] which are never seen in new lesions not modified by constant scratching.

PATHOGENIC CONSIDERATIONS

The first Europen authors who studied prurigo of Hebra considered it "angioneurosis" or "hematogenous inflammation." This is not explanatory, since these names hardly have meaning. The complex causation of prurigo of Hebra differs in certain cases and must

Fig. 3.—Photomicrograph of a biopsy specimen of a papule from the back twenty-four hours after its appearance. Neutrophil node with central leukolysis (hematoxylin and eosin stain).

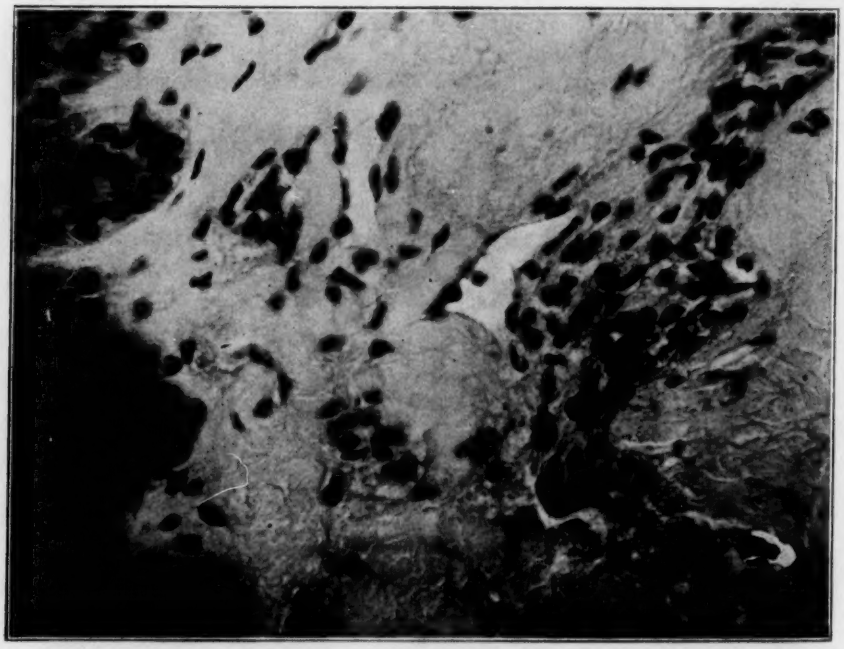

Fig. 4.—Photomicrograph of a biopsy specimen of a papule, ten days old, taken from a buttock. There was gradual replacement of neutrophils by lymphocytes and connective cells (hematoxylin and eosin stain).

be correctly evaluated in toto. The factor of importance is familial disposition; environment was proved to be also important by Jadassohn[13] and Barber.[14]

The existence of early lesions of strophulus and urticaria and "hemoclastic shock" (Lutz[18] and Brack[26]), the importance of metabolic and nutritional factors, and the possibility of oneset because of alimentary infections or inhalant allergens, demonstrable by positive reactions to cutaneous tests and by elimination and reexposure, cold and heat, are significant and allow us to classify prurigo of Hebra as an allergic (atopic) disease.

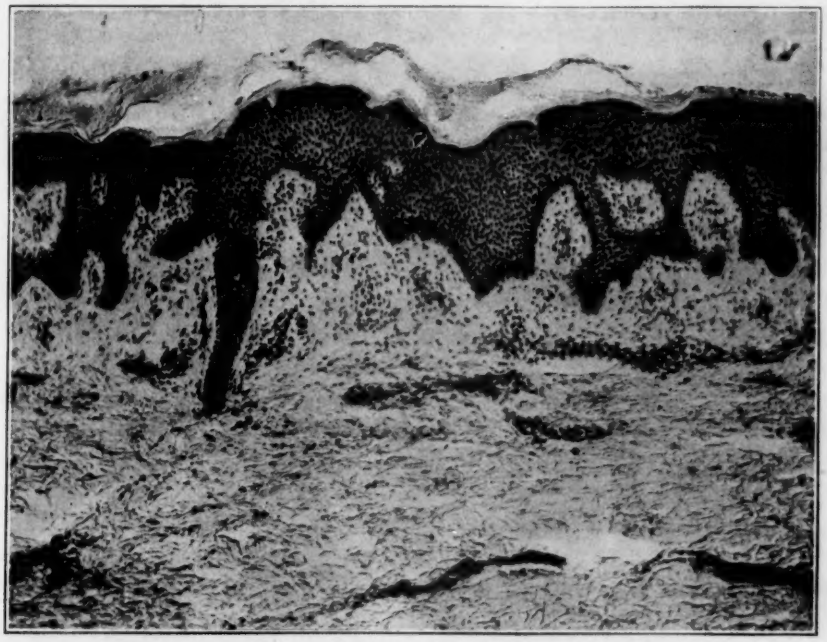

Fig. 5.—Photomicrograph of a biopsy specimen of a lichenified zone of the thigh. The epidermis was acanthotic; perivascular infiltrates in the papillary aspect of the dermis and the corium, made up chiefly of lymphocytes, can be seen (hematoxylin and eosin stain).

In addition, excellent results were obtained in our patient and in Noussitou and Cordero's patient[6] with an antihistaminic agent, diphenhydramine hydrochloride ("benadryl hydrochloride" N.N.R.). This also is in favor of the allergic causation of prurigo of Hebra.

The integrity of the peripheral nervous system seems to be fundamental in the appearance of prurigo of Hebra. Bernhardt[27] noticed that the peculiar eruption of prurigo of Hebra was not present on

26. Brack, L., cited by Lutz.[18]

27. Bernhardt, R.: Zur Pathogenese der Prurigo, Ach. f. Dermat. u. Syph. **57**:175, 1901.

the paralyzed arm of a patient because of secondary atrophy caused by poliomyelitis.

TREATMENT

Hygienic measures are all-important in the treatment of prurigo of Hebra. Jadassohn[13] and Barber[14] proved that the elimination of unfavorable environmental factors is of utmost importance. Therefore, hospitalization or change of climate is advisable for patients with the disease.

Diet must be carefully supervised. Large amounts of vitamins A and D, ferrous salts and calcium are recommended.

Local measures, such as daily bathing and careful treatment of impetigo and eczema with the ordinary methods, are absolutely necessary.

General treatment, such as arsenotherapy, is suggested. Both our patient and Noussitou and Cordero's patient[6] received a pentavalent arsenical ("acetylarsan" [diethylamine acetarsone]) in doses of 3 cc., twice a week, for several weeks, which seemed to improve their general condition. Gain in weight, the net psychic improvement and the influence on sleep were observed.

Diphenhydramine (150 to 250 mg.) was given daily for many weeks. During that time pruritus practically disappeared, the patient slept well and general improvement of the condition of the skin followed the relief of itching and desisting from scratching. No accidents followed the administration of this drug during long intervals. Occasional reports of improvement of pruritus and papules with treatment with roentgen rays have been made. However, it is doubtful whether roentgen rays are of any value in treatment for prurigo mitis (Mackee and Cipollaro[28]).

SUMMARY AND CONCLUSIONS

In this paper a case of prurigo ferox, or agria, of Hebra is reported. Clinical, histologic, causative and pathogenic factors are noted. According to these, prurigo ferox of Hebra must be considered an allergic disease, intimately related to familial disposition and environmental factors, of which lack of hygiene and malnutrition are particularly important.

Prurigo of Hebra should not be considered incurable; elimination of unfavorable environmental factors and adequate nutrition, supplemented with general measures and local treatment, contribute to improvement.

A report is made of a white girl, 6 years of age, in whom the disease was favorably influenced with general and local treatment. The favorable effects of treatment with diphenhydramine hydrochloride ("benadryl hydrochloride" N.N.R.) are reported.

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28. MacKee, G. M., and Cipollaro, A.: X-Rays and Radium in Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946, p. 440.

SITES OF DEPOSITION OF SILVER IN ARGYRIA

With Special Reference to the Axillary Glands

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BECAUSE of its accompanying cutaneous discoloration, argyria has dermatologic significance. Consequently, some attention has been given to the distribution of silver deposits in the skin of patients with argyria, but, in general, these studies have not included the large specialized sweat glands seen in the axillary and circumanal regions, which are usually regarded as being apocrine in secretory type. It has been noted that silver tends to be deposited in the subepidermal connective tissues, the connective tissue covering the sebaceous and small sweat glands, the perimysium, perineurium, the walls of blood vessels and the arrectores pilorum muscle.[1] The importance of the small sweat glands in this disease may be indicated by the suggestion of Firth and Harrison[1c] that silver is deposited first in the connective tissue surrounding them before it appears in some of the other locations. Only Riemer[2] studied the large axillary sweat glands in a patient with argyria, and he observed a considerable amount of silver between the cells of the connective tissue membrane surrounding these glands. During the course of a general study of the cells of the axillary glands, a patient with diffuse argyria came to our attention. Since some of our observations on the distribution of silver in her axillary skin are at variance with previous reports, we are submitting this information.

From the Departments of Dermatology and Syphilology and Anatomy, University of Michigan Medical School, Ann Arbor.

1. (*a*) Frommann, C.: Ein Fall von Argyria mit Silberabscheidungen im Darm, Leber, Nieren und Milz, Virschows Arch. f. path. Anat. **17**:135, 1859 (*b*) Kanitz, H.: Ueber Argyrie der Haut, Arch. f. Dermat u. Syph. **94**:49, 1909 (*c*) Firth, D., and Harrison, G. A.: A Case of Argyria, Brit. J. Dermat **36**:105, 1924 (*d*) Hill, W. R., and Montgomery, H.: Argyria with Special Reference to the Cutaneous Histopathology, Arch. Dermat. & Syph. **44**:588 (Oct.) 1941 (*e*) Harker, J. M., and Hunter, D.: Occupational Argyria, Brit. J. Dermat. **47**:441, 1935 (*f*) Lenartowicz, J., and Jalowy, B.: Essais de production d'argyrie artificielle chez les animaux, Ann. de dermat. et syph. **9**:483, 1938.

2. Riemer, B.: Ein Fall von Argyria, Arch. d. Heilk. **16**:296, 1875.

TECHNIC

The patient studied was a 56 year old white woman who, prior to examination, had taken silver nitrate orally for relief of gastric ulcer. Pieces of her axillary skin, secured in biopsy, were fixed in 10 per cent neutral formaldehyde and embedded in paraffin. The silver deposits in some sections were studied in nonstained preparations after clearing in xylene. Other sections were counterstained lightly with eosin and methylene blue. In some specimens an attempt was made to darken the silver further by treatment of the tissue with mercuric chloride and ammonium sulfide, as recommended by Firth and Harrison. These preparations were controlled by removing the silver from other sections with a solution of potassium ferrocyanide and sodium thiosulfate and also by examination of them with dark field illumination (Habermann[3]). The dark field method causes the silver deposits to appear as shiny bodies and according to some observers reveals more silver than can be seen with transmitted light. Parallel studies were made of the distribution of elastic and collagenous connective tissue fibers by staining sections, consecutive to those used in the observation of silver, with Weigert's elastic connective tissue and Masson technics.

OBSERVATIONS

In contrast to the report of Riemer,[2] little silver could be seen in the membrana propria of the large axillary sweat glands. With the oil immersion objective, only occasional areas showed minute indistinct granules of silver (*B* of the figure). This was true even after intensification with the method described in the preceding paragraph. Most of the membrana propria failed to show any silver with transmitted light or with the dark field illumination method.

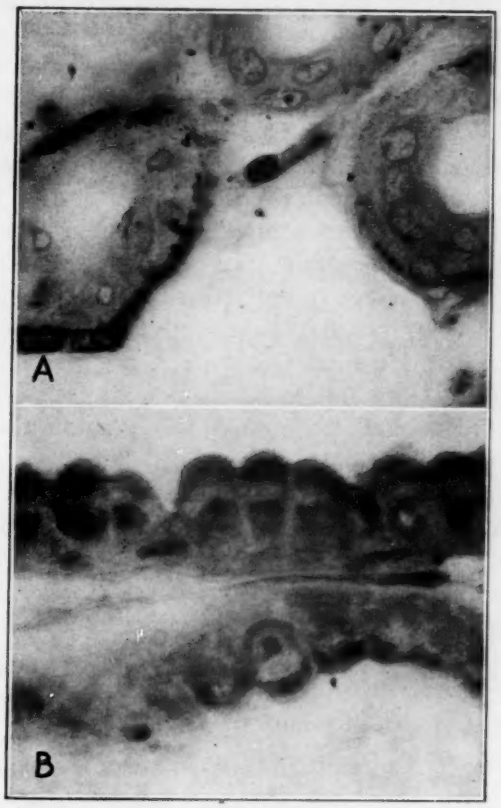
The small sweat glands of the axilla exhibited an entirely different picture. Striking concentrations of silver granules (*A* of the figure) were present in the connective tissue surrounding the secretory portion of the ordinary small sweat gland tubule. This was true of almost all of these glands in our specimen. The ducts, however, showed considerably less silver than the secretory tubules.

We next sought for an explanation of this difference in the affinity of silver for the connective tissue covering of the two types of sweat glands. It has been shown that silver tends to be deposited on elastic fibers more than on other structures.[4] Consequently, the connective tissue covering the small sweat and large axillary glands was stained with Weigert's elastic stain and examined for elastic fibers. We observed that the secretory portion of the small sweat gland was surrounded by a dense feltwork of fine elastic fibers, whereas, the membrana propria of the large axillary glands was associated with

3. Habermann, R.: Ueber Argyria cutis nach Silbersalvarsan und der Wert der Leuchtbildmethode E. Hoffmans für ihren Nachweiz, Dermat. Ztschr. **40**:65 1924.

4. Konitz.[1b] Blaschko, A.: Ueber physiologische Versilberung des elastischen Gewebes, Arch. f. mikr. Anat. **27**:651, 1886. Dohi, S.: Ueber Argyrie, Virchows Arch. f. path. Anat. **193**:148, 1908.

only a few scattered fine elastic fibers. With the Masson technic the membrana propria of the large axillary glands was stained with aniline blue, demonstrating the presence of collagenous or reticular connective tissue fibers. Also, the Weigert technic for elastic connective tissue revealed fine sparsely scattered elastic fibers in close association with the external surface of the myoepithelial cells. The structure of the membrana propria will be analyzed more fully in a



Intensification with ammonium sulfide (eosin methylene blue stain + 720): *A*, the secretory portion of a sweat gland, showing silver granules (black) in the surrounding connective tissue. The ducts at the right and above possess less silver. *B*, two axillary glands, the membranae propriae of which are in contact with each other. The only silver deposits which are visible are a few minute granules scattered along the ouside of the membranes.

future report. The difference in concentration of elastic fibers in the enveloping connective tissue of the two types of glands was striking and constant. Thus, there is a direct correlation between the amount of silver deposited and the density of the elastic fibers in the surrounding connective tissue. This may explain the difference in the affinity of silver for the large axillary and small sweat glands.

In respect to the other sites of deposition, our observations are in good agreement with present opinion. Fine granules of silver

formed an inconstant border beneath the epidermis in the loose connective tissue of the papillary layer. Larger granules were scattered more sparsely throughout the corium and by observation at high magnification, smaller granules were seen to speckle the broad elastic fibers of this layer. The presence of silver in the corium is especially impressive when viewed with dark field illumination. Considerable accumulation of silver also occurred in the connective tissue surrounding the sebaceous glands and certain parts of the hair follicle and in the arrectores pilorum muscle.

Considerable disagreement exists concerning the occurrence of silver within cells. Its presence was reported within endothelial cells,[5] fibroblasts[6] and mast cells.[5b] Cascos,[5c] however, denied the occurrence of silver within fibroblasts or mast cells. In our preparations, the fibroblasts did not reveal silver.Only one or two were observed which might have contained a little silver, but the identification of these cells was open to question. Mast cells were numerous, and many were so densely granulated when stained with methylene blue that the absence of silver could not be determined with certainty. In those cells which did not contain such dense granulation no silver was seen. Similarly, no silver was seen in mast cells when these cells were not counterstained. Dark field illumination revealed minute shiny bodies in the region of mast cells, but these seemed to be extracellular in position. We were unable to locate silver within the endothelium of capillaries. It was present in the walls of small arteries and veins, but it was impossible to determine the precise location of the silver in relation to the constituent cells. Silver was identified definitely within connective tissue macrophages and dermal chromatophores. The dark field method has been used by most workers reporting on the intracellular position of silver. In our experience this method has definite limitations in determining whether silver is deposited within cells.

SUMMARY

In a study of the distribution of silver deposits in a patient with argyria, it was observed that the membrana propria of the large axillary sweat glands contained little silver in contrast to the dense concentrations of silver in the connective tissue surrounding the small sweat glands. This deposition of silver seemed to be directly related to the difference in concentration of elastic fibers in the connective tissue enveloping the two types of glands.

5. (*a*) Habermann.[3] (*b*) Zoon, J. J.: Ueber histologische Befunde bei Argyria cutis, Dermat. Ztschr. **70**:125, 1934. (*c*) Cascos, M. A.: Etude comparative des figmentations metalliques; Argyrose et chrysose, Ann. de dermat. et syph. **7**:751, 1936.

6. Kantz.[1b] Zoon.[5b]

FAMILIAL STEATOCYSTOMA MULTIPLEX

Twelve Cases in Three Generations

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AND
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COCKAYNE[1] has reported that the occurrence of steatocystoma multiplex is rare. In 1937 Ingram and Oldfield[2] reported that there were on record only five families in which several members in different generations had multiple sebaceous cysts. Subsequently the incidence in additional families has been reported. Ingram and Oldfield reported the incidence of the disease in an additional family, involving 5 members in three generations, in which 1 member had numerous swellings on her face and chest. Her daughter was free of this condition, but her son showed several cysts on his forehead and scalp. Of the son's 7 children (5 sons and 2 daughters), 2 sons and 1 daughter had sebaceous cysts. The other 4 children did not have cysts.

Sachs[3] reported a family of 13 in which 2 sisters and 3 brothers were known to have multiple sebaceous cysts. Two other living members of the family were free of them. It was not known whether any of the 6 deceased children had exhibited cysts. The father of these 13 children and his sister showed cysts. A brother was not affected. Two affected siblings of the family of 13 had children showing cysts, but each also had a normal child. The members of this family with the disease were said to have been affected from birth.

Munro[4] and Cockayne have suggested that multiple sebaceous cysts are transmitted by a single dominant mendelian factor, and the

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From the Section on Dermatology and Syphilology of the Department of Medicine, Medical College of Alabama (Dr. Noojin), and the Genetics Division, Department of Biology, Birmingham-Southern College (Dr. Reynolds).

1. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933, p. 352.

2. Ingram, J. T., and Oldfield, M. C.: Hereditary Sebaceous Cysts, Brit. M. J. **1**:960-963 (May 8) 1937.

3. Sachs, W.: Steatocystoma Multiplex Congenitale: Ten Cases in Three Generations, Arch. Dermat. & Syph. **38**:877-880 (Dec.) 1938.

4. Munro, T. A.: Hereditary Sebaceous Cysts, J. Genetics **35**:61-72 (Oct.) 1937.

former has suggested that in homozygous form the effect may be so serious as to be "incompatible with life." This suggestion was based on the occurrence of the abnormality in 3 children who died in infancy and whose father and mother were both affected. Ingram and Oldfield also stated that the family reported by them seemed to exhibit a factor for multiple cysts inherited in a dominant rather than a recessive mendelian fashion.

Munro has also suggested that there may be some genetic relationship between sebaceous cysts and maligant growths, in view of the fact that in 1 of his family cases, both maladies occurred in considerable numbers.

When a patient of one of us (R.O.N.) was observed to have numerous sebaceous cysts and reported that her mother and other members of the family were similarly affected, an investigation was made of as many members of this family as possible. It was felt that an additional family history might add more information regarding

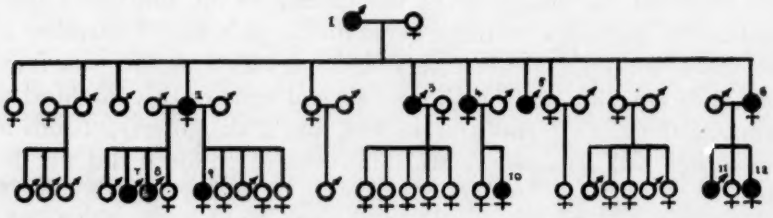

Fig. 1.—Genealogic chart (dark areas show those affected): 1 is the grandfather; 2, the patient's mother; 3, the patient's uncle; 4, the patient's aunt; 5, the patient's uncle; 6, the patient's aunt; 7, the patient's half-brother; 8, the patient's half-brother; 9, the patient; 10, the daughter of the patient in case 4; 11, the son of the patient in case 6, and 12, the daughter of the patient in case 6.

the problem of inheritance of sebaceous cysts. Further, additional inquiry might be made regarding a relationship between these cysts and malignant neoplasms. Several laboratory studies of the original patient were carried out.

The members of the aforementioned family lived in Alabama, Mississippi and Tennessee. Our information regarding the occurrence of cysts was derived primarily through personal observation. Some of the affected members of this family were not living; therefore, it was necessary to rely on living members for information concerning them. Figure 1 indicates the frequency of occurrence of cysts in this family. It shows only three generations. However, at least 56 fourth generation children were living as of the time of writing. They ranged in age from infancy to 21 years. Five of them were offsprings of an affected parent. As this report was prepared no cysts had occurred in the fourth generation.

REPORT OF A CASE

J. S., a 36 year old Negro woman, stated that as far back as she could remember her body had been covered with numerous "lumps." There had been no local discomfort except that at times a single lesion would "come to a head like a boil," rupture and exude a whitish substance. In recent years the patient had not noted any new lesions. She was not aware that any of the lesions had increased in size during the past twenty years. The family history revealed no positive history of familial disease other than the fact that numerous members of the family had multiple sebaceous cysts. Table 1 lists in chronologic order the affected members. No history of cancer was elicited from any member of this family.

Physical Examination.—Physical examination revealed a poorly nourished patient who had on her body numerous oval elevated moderately firm doughy tumors, varying in diameter from 1 to 5 cm. The lesions were distributed as follows: seventeen were on the head, forty on the neck, sixty-five on the trunk, one hundred on the arms and thirteen on the legs. Grossly none of the tumor surfaces revealed the presence of follicular plugging. Examination revealed no other abnormalities.

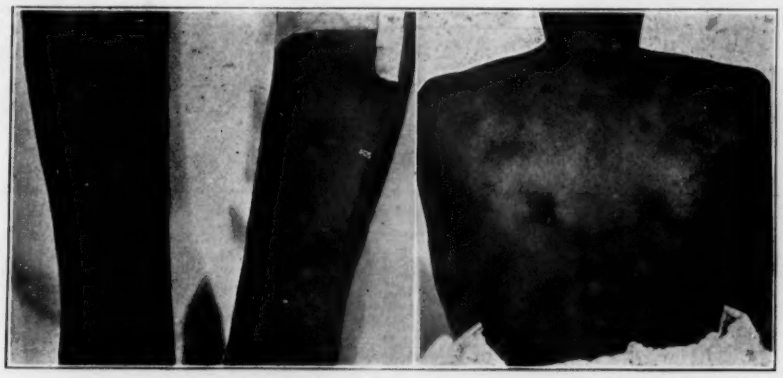

Fig. 2.—J. S., the patient in the third generation of those affected.

Accessory Clinical Data.—The patient had a red blood cell count of 4,330,000 per cubic centimeter; the hemoglobin determination was 13 Gm., or 84 per cent (Haden-Hauser); the color index was 0.97; the white blood cell count, differential formula and results of urinalysis and repeated serologic tests for syphilis were not remarkable. Determinations of the chemical content of the blood are shown in table 2. The results of a glucose tolerance test are recorded in table 3. Roentgenograms of the chest, right hand and foot revealed no abnormalities.

The pathologic report on one of the lesions removed for biopsy revealed a cyst the wall of which was lined by thin stratified squamous epithelium. The epidermis was normal. No evidence of chronic inflammation was present. Serial sections were examined, and several consecutive sections revealed the presence of remnants of a sebaceous gland within the wall of the cyst. No evidence of an occluded sebaceous duct or follicular orifice was seen.

COMMENT

Our data appear to substantiate the fact that multiple sebaceous cysts may be inherited and that the factor responsible is a single dominant mendelian factor. Cysts have occurred in three generations, and

TABLE 1.—*List of Cases, Showing Relationship, Age, Number of Cysts and Time of Appearance of Cysts*

Case No.	Relationship	Age (Yr.)	Number of Cysts	Time of Appearance
1*	Patient's grandfather	Died at 80	Many	Childhood
2†	Patient's mother	65	Many	Childhood
3*	Patient's uncle	55	Many	Childhood
4*	Patient's aunt	Died at 40	Few	Childhood
5*	Patient's uncle	Died at 40	Few	Childhood
6†	Patient's aunt	46	Many	Childhood
7†	Patient's half-brother	43	Many	Childhood
8†	Patient's half-brother	42	Few	After 30
9†	Patient	36	Many	Childhood
10*	Daughter of patient in case 4	27	Few	Childhood
11*	Son of patient in case 6	25	Many	Childhood
12†	Daughter of patient in case 6	20	Few	Childhood

*The patient was not seen; information was obtained from other members of the family.
†The patient was examined.

TABLE 2.—*Determinations of the Chemical Content of the Blood (Fasting)*

Substance	Values	
Cholesterol	221	Mg. per 100 cc. serum
Total serum proteins	7	Mg. per 100 cc. serum
Albumin	3.50	Mg. per 100 cc. serum
Globulin	3.49	Mg. per 100 cc. serum
A/G ratio	1:1	
Vitamin A	83	U.S.P. units per 100 cc. plasma
Carotene	217	U.S.P. units of vitamin A per 100 cc. plasma
Vitamin C	0.391	Mg. per 100 cc. plasma
Vitamin E	0.64	Mg. per 100 cc. plasma

TABLE 3.—*Results of Glucose Tolerance Test**

Specimen	Glucose (Mg. per 100 Cc. Blood)	Sugar in Urine
Fasting	79	None
30 min.	130	None
1 hr.	162	None
2 hr.	102	None
3 hr.	58	None

*One hundred grams of dextrose were given to the patient orally after collecting fasting specimens.

in each case of their occurrence 1 parent was affected. If the factor responsible for development of the cysts is a single dominant one, the ratio of affected to nonaffected persons in families with 1 affected parent theoretically should be 1 to 1. In this family the ratio was 11 to 18. In one second generation family of 5 girls (daughters of an affected father), not any showed cysts. These daughters were between 20 and 30 years of age, and it is possible that in some members of that particular group cysts may yet develop.

No suggestion of the factor's being sex linked or sex influenced can be found in this family. The ratio of male to female members affected is 1 to 1. Mount[5] stated that in previously reported cases

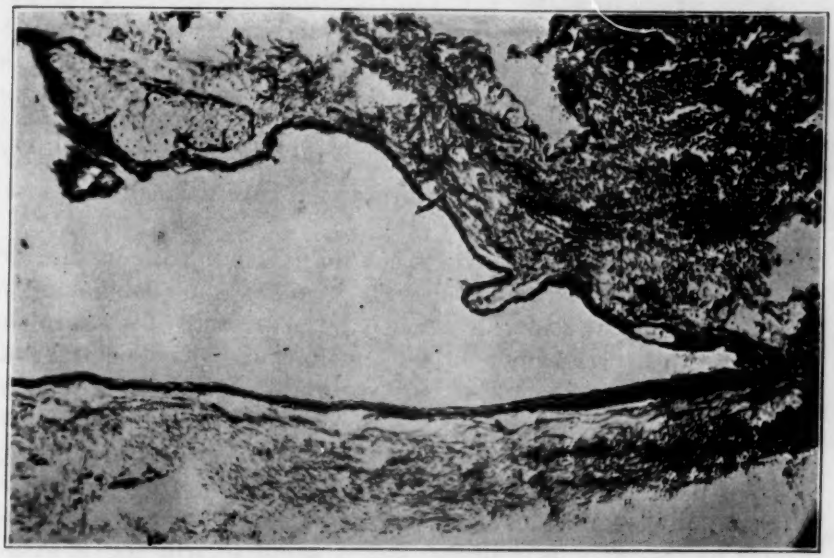

FIG. 3.—Photomicrograph (× about 32) showing a cyst in the dermis. Remnants of a sebaceous gland may be seen within the wall (upper left) of the cyst.

male members were more frequently involved than female members, the ratio being 3 to 1. Sachs observed that in his series as many women were affected as men.

The age at which cysts developed varied from early childhood to over 30 years. In the majority of the affected persons cysts developed between the ages of 12 and 18 years. In persons with many cysts the lesions tended to develop at a younger age than in those with only a few cysts.

No evidence of malignant growth was elicited in any member of the family herein reported.

There is a difference of opinion as to the causation of multiple

5. Mount, L. B.: Steatocystoma Multiplex, Arch. Dermat. & Syph. **36**:31-39 (July) 1937.

sebaceous cysts. The more recent articles of Ormsby and Finnerud,[6] Ingram and Oldfield and Mount discussed in detail their own observations as well as those in earlier publications. Ingram and Oldfield pointed out that the cysts had usually been regarded by previous investigators as either (1) due to retention within the pilosebaceous structure or (2) cysts of new formation. They expressed opinion in favor of the latter view. They listed the following facts as evidence against the retention theory: the rarity of cyst formation in cases of severe acne, the rarity of comedos in cases of sebocystomatosis, the difficulty of demonstrating by serial section an occluded or partially obliterated sebaceous duct and the occurrence of cysts of identical histologic structure on the palms of the hands and the volar surfaces of the fingers, sites devoid of sebaceous glands and hair follicles. Although Ormsby and Finnerud were able to show microscopically how cysts had apparently been caused by plugging of the pilosebaceous follicular orifice, the plugging in these instances may have been either incidental or may have been effect rather than cause. Follicular plugging occurs in other dermatoses which do not have the feature of local formation of sebaceous cysts.

The laboratory results carried out for 1 of our patients did not appear to be significantly abnormal. There was no laboratory or clinical evidence of vitamin A deficiency, the presence of which might predispose to hyperkeratosis, subsequent follicular plugging and possible blockage of the pilosebaceous apparatus. Histologic studies of cysts from members of the family herein reported added no additional pathologic observations not previously described. No follicular plugging was noted even when serial sections were made. It would appear that familial cysts might well be due to some genealogic defect, as indicated by observations in studies similar to the present one. It would not seem illogical to assume that with familial cysts the formation may be due to some transmitted anatomic or lipid metabolic abnormality, particularly since several families have shown a responsible single dominant mendelian factor.

SUMMARY AND CONCLUSIONS

A report is made of the occurrence of familial steatocystoma multiplex in 12 members of a single family in the course of three generations. The factor which determines multiple sebaceous cysts is a dominant rather than a recessive character. In view of the familial tendency which may occur, it seems logical to assume that multiple sebaceous cysts may develop because of transmitted abnormalities occurring within the pilosebaceous apparatus. There appears to be no increased incidence of malignant neoplasms in families with familial steatocystoma multiplex.

6. Ormsby, O. S., and Finnerud, C. W.: Steatocystoma Multiplex, Arch. Dermat. & Syph. **22**:822-832 (Nov.) 1930.

TRIBROMOETHANOL ("AVERTIN") IN THE TREATMENT OF NEURODERMATOSES

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IN MY experience, the accepted treatment for the management and treatment of neurodermatoses, consisting of topical applications, attention to the patients' general and nervous status, roentgen irradiation, sedation and psychotherapy, has produced satisfactory results in only a small percentage of the cases. The subsequent recurrence and ultimate failure of recognized treatment to relieve these patients prompted this study. This report, therefore, is concerned with the consideration of another therapeutic approach, the use of a basal anesthetic, solution of tribromoethanol ("avertin with amylene hydrate"), which is tribromoethyl alcohol (CH_2CH_2OH).

The use of anesthesia in the treatment of cutaneous disorders has been receiving considerable attention in the current literature. The principle is, however, not new. In the early part of the nineteenth century, sedation with opium and ether and chloroform by inhalation and rectal injection was employed in the treatment of mental illness. In the early part of the twentieth century, chloral and bromides were used, to be followed later by the use of the barbiturates, which facilitated continuous sleep as a form of treatment. Lundy[1] reported the successful use of procaine hydrochloride intravenously in providing relief from pruritus in patients suffering from intractable jaundice. Gordon[2] was able to relieve pain associated with burns with the same method. State and Wangensteen[3] and Applebaum and his co-workers[4]

From the Department of Dermatology and the University of Pittsburgh School of Medicine.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 4, 1947.

1. Lundy, J. S.: Clinical Anaesthesia, Philadelphia, W. B. Saunders Company, 1942, pp. 392-393.

2. Gordon, R. A.: Intravenous Novacain for Analgesia in Burns, Canad. M. A. J. **49**: 479 (Dec.) 1943.

3. State, D., and Wangensteen, O. H.: Procaine Intravenously in Treatment of Delayed Serum Sickness, J.A.M.A. **130**:990 (April 13) 1946.

4. Applebaum, E.; Abraham, A., and Senton, W.: A Case of Serum Sickness Treated with Procaine Intravenously, J.A.M.A. **131**:1274 (Aug. 17) 1946.

reported that procaine hydrochloride injected intravenously was extremely effective in the treatment of delayed serum sickness and urticaria. Allen and his associates[5] broadened the field of intravenous procaine hydrochloride therapy by administering the drug to patients with a wide variety of painful conditions. Frostbite of the extremities[6], herpes zoster[7] and various vascular disturbances of the extremities have been successfully treated with paravertebral injections of procaine hydrochloride. The use of alcohol injections in the treatment of localized neurodermatitis has recently been reported by Pels and Ellis[8]. Strickler[9] used cocaine hydrochloride intraspinally in the treatment of pemphigus. MacCormac, Sandifer and Jelliffe[10] reported the results of continuous narcosis therapy in the treatment of a group of diethyl and allylisopropyl-barbituric acid (supplemented by paralani et vulvae, generalized pruritus, psoriasis and exfoliative dermatitis. Sleep was induced for twenty out of twenty-four hours for periods up to two weeks by the use of "somnifaine" (solution of diethylamine salt of diethyl and allylisopropyl-barbituric acid) supplemented by paraldehyde. The treatment is dangerous unless properly performed and administered under carefully selected conditions. Adequate nursing care and experience with this method are necessary to avoid possible lethal accidents and to secure peaceful sleep of sufficient depth and duration to produce the desired therapeutic results. Most patients were relieved to a greater or lesser degree, by the control of almost unbearable pruritus, and the authors expressed the opinion that the improvement was only relative. Netherton[11] used procaine hydrochloride intravenously in the treatment of 4 patients with generalized neurodermatitis. He observed this type of treatment to be beneficial. The improvement was not apparent until treatment was carried on for four to five days, after which the pruritus subsided materially, and in all cases disappeared for several days. He expressed the opinion that these patients, on discharge, were in better condition than patients with similar disease that had been hospitalized and treated with other

5. Allen, F. M.; Crossman, L. W., and Lyons, L. V.: Intravenous Procaine Analgesia, Anesth. & Analg. **25**:1 (Jan.-Feb.) 1946.

6. Buck, F.: Procaine Hydrochloride Infiltration of Lymphathetic Nerve in Early Frost Bite of the Extremities, Chirurg **15**:347 (June 15) 1943.

7. Findley, T., and Patzer, R. J.: Treatment of Herpes Zoster by Paravertebral Procaine Block, J.A.M.A. **128**:1217 (Aug 25) 1945.

8. Pels, J., and Ellis, F. A.: Circumscribed Neurodermatitis (Lichen Chronicus Simplex): Its Treatment by Injection of Alcohol, Arch. Dermat. & Syph. **54**:677 (Dec.) 1946.

9. Strickler, A. S.: Personal communication to the author.

10. MacCormac, H.; Sandifer, P. H., and Jelliffe, H. M.: Itchy Patient, Brit. M. J. **2**:48 (July 13) 1946.

11. Netherton, E. W.: Personal communication to the author.

means. He encountered no toxic symptoms, but cautioned against the possibility of phlebitis. Curtis,[12] at my suggestion, used solution of tribromoethanol ("avertin") in the treatment of 1 patient with pruritus ani and 1 patient with generalized neurodermatitis. He commented that both patients received almost complete relief from paroxysms while under the effects of the drug, and he stated the belief that it had value in this type of disease. Sulzberger[13] experienced disappointing results with continuous narcosis as well as electric shock therapy and psychiatric approaches. The purpose of this study was to seek relief for these patients from the distressing and uncontrollable pruritus and to ease the accompanying mental anxiety so commonly associated with neurodermatoses. In order to accomplish this, it was necessary to secure sufficient sleep and complete relaxation. Since it is generally agreed that sedation is beneficial in alleviating pain and itching, it seemed plausible that narcosis induced by an anesthetic might be effective in arresting these difficult and intractable symptoms. Tribromoethanol was chosen because of its particular value as an anesthetic in highly nervous patients. It has been successfully administered as symptomatic treatment in asthmatic crises,[14] tetanus[15] and excited states in patients with psychopathic personality[16]. Its administration is simple; it may be given in the ward or in the patient's room; it produces gradual and peaceful sleep, and the awakening is equally so. The resultant lack of memory of anything from the time of injection and the ability of the drug to produce light or deep sleep made it suitable for the purpose for which it was chosen. The distention, nausea and vomiting commonly associated with other anesthetics is uncommon, and fluids and food may be given soon after the awakening. The use of tribromoethanol, however, requires careful selection of the patient, the direct supervision of a trained anesthestist and adequate nursing facilities, in order to avoid serious accidents and to secure peaceful sleep of sufficient duration and depth to produce the desired therapeutic result. It is undesirable to attempt this type of treatment except under these conditions.

12. Curtis, A. C.: Personal communication to the author.

13. Sulzberger, M. B.: 1945 Year Book Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1946, pp. 118-119.

14. Fuchs, A. M.: The Interruption of the Asthmatic Crisis by Tribromethanol: Avertin, J. Allergy **8**:340 (May) 1937.

15. Cole, L.: The Treatment of Tetanus with Continuous Avertin Anaesthesia, Lancet **2**:246 (Aug. 3) 1935.

16. Livingstone, H., and Light, G.: The Anaesthetist Assists the Psychiatrists: Case Reports, Anesth. & Analg. **19**:349 (Nov.-Dec.) 1940.

METHOD

Each patient received complete medical study and was hospitalized for the duration of the treatment. The recognized contraindications to the use of tribromoethanol were observed. An elevation of over 50 mg. in the nonprotein nitrogen content of the blood contraindicated its use in this study. The time-honored quiet and darkened room was of importance, and the treatment was given during the early evening hours. Tribromoethanol fluid was used, 1 cc. of the fluid containing 1 Gm. of tribromoethanol and 0.5 Gm. of amylene hydrate. Solutions of the fluids were prepared according to the manufacturer's instructions in a 2.5 per cent solution in distilled water at a moderate temperature of from 95 to 104 F. (35 to 40 C.). No auxiliary medication was given. The solution was injected slowly, rectally, using a funnel with a male catheter. The fluid was introduced into the lowermost part of the bowel at a slow rate (five to ten minutes), avoiding force, as high and rapid injection, because its rapid absorption may "flood" the blood stream with the anesthetic and cause undue fall in blood pressure as well as respiratory depression. A cylinder of 10 to 90 mixture of carbon dioxide and oxygen, or oxygen and an airway, together with effective antidotes, as ephedrine sulfate or caffeine and sodium benzoate, was available to control any circulatory or respiratory complications or prolonged delay in return to consciousness. A period not exceeding seven days was chosen for the duration of the treatment. A dosage of 80 mg. per kilogram of body weight, which is the equivalent dosage used for anesthesia in general and special surgical treatment, was administered. Similar dosage in different patients was observed to vary in its anesthetic effect on the patient, and a higher metabolic activity frequently resulted in shorter periods of narcosis. This required a modification in a few of the patients by an increase or decrease of the dosage of 80 mg., as indicated by the apparent metabolic activity of the patient. The drug was absorbed rapidly, and its effects were manifested in a short period of time. It produced unconsciousness quickly and quietly within thirty minutes. The patient could be aroused and answered questions in the stuporous state or would awaken within three to four hours and doze off again into a peaceful sleep which lasted for several hours. During this period the patient was watched closely for any late effects of circulatory or respiratory depression. When the patient awakened none of the after-effects commonly observed with the use of other anesthetics were encountered. Nausea and vomiting were absent, and no irritation of the rectum was observed. The patient was allowed to be up and around until the next injection of tribromoethanol, and food and fluids were permitted as the patient desired after the awakening. No local application was used except petrolatum and then only on the request of the patient. Pruritus and mental anxiety were gradually eased by the successive injection of the drug, reached a maximum about the sixth day, and were maintained as recorded in the table. The exceptions occurred in 2 cases of neurotic excoriations and 1 case of urticaria, in which relief was evident only during the period of narcosis. Improvement in the appearance of the skin was noticeable after the fourth day and continued during the period of observation.

COMMENT

The accompanying table summarizes the clinical types in this study, duration of the disease, length of treatment and results obtained. Twenty patients were studied, including 11 patients with generalized neurodermatitis, 3 patients with pruritus ani et vulvae, 2 patients each with urticaria, neurotic excoriations and dermatitis her-

petiformis. The chronicity of these diseases is indicated by durations of two to twenty-two years. Of this group, 17 were women and 3 were men, with ages ranging from 19 to 59 years. All patients treated had failed to respond to other recognized treatment, including previous hospitalization. Eleven of the patients, whose disease was clas-

Summary of Data and Results of Treatment

Case No.	Age	Sex	Diagnosis	Duration of Disease (Yr.)	Treatment (Days)	Dosage (Mg. per Kg. of Body Weight)	Result
1	26	F	General disseminated neurodermatitis	19	6	60	Relief maintained 9 mo.
2	22	F	Neurodermatitis	4	7	80	Relief maintained 6 mo.
3	31	F	Neurodermatitis	8	6	80	Relief 4 mo.; recurrence
4	36	F	Neurodermatitis	2	6	80	Relief 3 mo.; recurrence
5	26	F	Neurodermatitis	2	6	80	Relief 3 mo.; recurrence
6	37	F	Neurodermatitis	2	6	80	Relief 3 mo.; recurrence
7	23	F	Neurodermatitis	5	6	80	Relief 3 mo.; recurrence
8	22	F	Neurodermatitis	12	6	80	Relief 6 wk.; recurrence
9	19	F	Neurodermatitis	7	6	80	Relief 2 mo.; recurrence
10	32	F	Neurodermatitis	22	6	80	Pruritus greatly reduced for 3 mo.; recurrence
11	23	M	Neurodermatitis	3	6	40-60	Relief 2 wk.; recurrence
12	59	M	Urticaria	2	6	80	Recurrence 4 hr. after cessation of treatment
13	42	F	Urticaria	2	7	80	Relief 6 mo.; no recurrence when last reviewed
14	46	F	Neurotic excoriations	2	4	40-60	Relief only during narcosis; immediate recurrence
15	42	F	Neurotic excoriations	6	4	40-60	Relief only during narcosis; immediate recurrence
16	42	F	Dermatitis herpetiformis	9	6	60	Relief 1 wk.; recurrence
17	34	M	Dermatitis herpetiformis	7	6	60	Relief 10 days; recurrence
18	36	F	Pruritus ani et vulvae	2	6	80	Relief 2 mo.; recurrence
19	38	F	Pruritus ani et vulvae	3	6	80	Relief 6 wk.; recurrence
20	46	F	Pruritus ani et vulvae	2	6	80	Relief 2 mo. when last reviewed

sified in the neurodermatitis group, were afforded most relief. Two patients were relieved for periods of six to nine months, respectively; 6 were relieved from three to four months; 3 were relieved for two months, six weeks and two weeks, respectively. The recurrences which were observed were milder than had previously been experienced. These patients expressed willingness to undergo another course of

treatment, should the occasion arise, and expressed gratification at being able to sleep. Some of these patients had not slept well for days or weeks at a time. The usual nervousness and excitement were greatly eased. Two patients with neurotic excoriations failed to receive any relief except during the stage of anesthesia, and there was recurrence immediately after the awakening. Treatment was discontinued after four days. These patients had previously received no benefit from psychotherapy and electric shock therapy. Two patients with urticaria had variable results. In one instance, recurrence was noted within four hours after cessation of a six day course of treatment. The other, however, had no recurrence for six months following the treatment. Two patients with dermatitis herpetiformis were treated, and the relief given, lasting only seven and ten days, respectively, did not justify further study in this disease. Three patients with pruritis ani et vulvae were relieved for periods of six weeks to two months, and recurrences were milder and were controlled more readily with supplementary therapeutic administration. On discharge, the patients were in better condition physically and mentally than patients with similar disease who were hospitalized and treated by other means.

It appears from this limited study that the patients with neurodermatitis and pruritus ani et vulvae reacted most favorably. Complete failure was recorded in the patients with neurotic excoriations and dermatitis herpetiformis. Relief in 1 case of urticaria was gratifying. The recurrences, as a rule, were milder in scope than in previous experiences and were relieved more readily by subsequent medication. The factors in common in the cases under study were uncontrollable pruritus, loss of sleep and mental anxiety. Although the treatment was symptomatic and the improvement manifested can be considered only relative, relief was afforded to the majority of the patients undergoing treatment. In this sense, the objective for the treatment was accomplished.

SUMMARY

A form of treatment is described which has provided relief in certain neurodermatoses. Twenty patients presenting generalized neurodermatitis, urticaria, pruritus ani et vulvae, neurotic excoriations or dermatitis herpetiformis were treated with tribromoethanol ("avertin in amylene hydrate"). No attempt was made to treat these patients by other means.

5026 Jenkins Arcade.

Dr. George J. Thomas, Department of Anaesthesia, University of Pittsburgh School of Medicine, gave suggestions in the preparation of this paper.

ABSTRACT OF DISCUSSION

DR. EARL W. NETHERTON, Cleveland: It was with much interest that I listened to Dr. Beinhauer's presentation, for I have known for two and a half years of his use of basal anesthesia in cases of severe disseminated neurodermatitis.

The dermatoses included in Dr. Beinhauer's report constitute some of the complex and frequently encountered dermatologic problems, in which management has been difficult and results have been far from satisfactory. Many patients with disseminated neurodermatitis have spent a large portion of their lives under the care of internists, allergists and dermatologists.

Many of these patients are now being advised to consult psychiatrists. A critical survey of therapeutic results obtained in the neurodermatoses shows that little progress has been made during the past decade.

The chief difficulty is a lack of a comprehensive knowledge of the causative mechanisms of disseminated neurodermatitis. There is divergence of opinion regarding the relative causative importance of psychogenic and allergenic factors. For many year sedatives have had an important role in the management of neurodermatoses. Patients complaining of intolerable and uncontrollable pruritus, with resulting loss of sleep and mental anxiety, require, among other measures, hospitalization and heavy sedation.

It is for this type of patient that Dr. Beinhauer advocates the use of tribromoethanol ("avertin with amylene hydrate") anesthesia. The procedure which he describes might be considered heroic; however, distress caused by itching and insomnia is often so severe that the patient welcomes the relief obtained with basal anesthesia.

The need for careful selection of cases, adequate nursing facilities and direct supervision by a trained anesthetist, to avoid serious accidents and to obtain desired therapeutic results, has been emphasized. The inability of many hospitals to provide these technical requirements will, for the present, prevent general use of this therapeutic procedure. I have been anxious to try tribromoethanol anesthesia as advocated by Dr. Beinhauer. However, the current shortage of trained nurses has made this impossible.

Dr. Beinhauer has referred to the use of procaine hydrochloride in the treatment of neurodermatoses. It may be that analgesia from the intravenous administration of procaine hydrochloride will be of value for recalcitrant neurodermatoses. It has been used successfully for the relief of itching of jaundice, delayed serum sickness and pain from burns, childbirth and other conditions.

Intravenous administration of procaine hydrochloride is relatively safe and does not present technical problems as difficult as does basal anesthesia. Circulating procaine hydrochloride is counteracted rapidly in the liver; consequently, toxic reactions are few and can readily be controlled by regulation of the rate of administration of the drug. Furthermore, procaine hydrochloride readily permeates edematous and inflamed tissue, and, since its main action is on peripheral nerves, relief of pain and pruritus can be obtained without narcosis. There are other theoretic pharmacologic properties of procaine hydrochloride which justify its investigation along the lines advocated by Dr. Beinhauer.

During the past year my associates and I have used procaine hydrochloride intravenously in 5 cases of refractory atopic dermatitis and at present are using it in another case. A patient with a serum-sickness-like reaction due to penicillin was also treated.

The technic was carried out in collaboration with Dr. D. E. Hale, chief of the department of anesthesia at the Cleveland Clinic Hospital, with 0.5 per cent

procaine hydrochloride in isotonic solution of sodium chloride or 5 per cent dextrose given intravenously by continuous drip. The inital rate of flow was 10 drops a minute. The rate of flow was gradually increased until itching ceased or materially decreased.

There was prompt relief of pruritus within fifteen minutes, provided that the drug was given at the rate of 20 to 30 drops per minute. However, itching returned within an hour when medication was stopped.

From 2.5 to 4 Gm. of procaine hydrochloride were given within twenty-four hours. One patient received 43 Gm. of procaine hydrochloride in seven days. Another received 30 Gm. in ten days. Pruritus between infusions did not decrease materially before the fourth or fifth day. We observed no systemic reactions, but in 3 patients phlebitis developed.

Infusions with procaine hydrochloride were discontinued from the seventh to the tenth day of treatment. Itching was tolerable, and insomnia was no longer troublesome. The patients remained in the hospital two to four weeks after infusions were discontinued. Phenobarbital was given at night, and boric acid ointment was applied twice a day.

When discharged from the hospital, all patients were able to sleep and complained little of itching. In 1 case there was recurrence of severe pruritus within two weeks; 1 patient has disappeared from observation, and 3 have remained free of recurrence of severe pruritus. Two patients have recently been observed six months after discharge from the hospital, and both stated that itching had been less severe than in many months. The serum-sickness-like reaction due to penicillin responded favorably to the intravenous administration of procaine hydrochloride.

We observed that the pruritus of disseminated neurodermatitis can be eliminated temporarly and or abated for a period of time by the intravenous administration of procaine hydrochloride. However, a large series of patients with shorter hospitalization must be studied and technics improved before any conclusion can be reached regarding the value of this procedure for neurodermatoses.

Dr. Beinhauer has been conservative in the interpretation of his results and advocates the use of tribromoethanol anesthesia only as an adjunct to the treatment in selected cases of neurodermatoses. His results were superior to those usually secured with older accepted measures. Cures were not obtained, but recurrences were longer delayed and less severe.

Dr. Beinhauer is to be congratulated on being, so far as I know, the first to study the use of basal anesthesia for relief of symptoms in selected cases of neurodermatitis. There is a definite need for the treatment which he advocates, and it deserves further study.

Dr. S. William Becker, Chicago: I believe that the results reported by Dr. Beinhauer in neurodermatoses are phenomenal. However, it is possible to obtain equally good results with the use of barbiturates. If the paitent can be hospitalized, it is possible to relieve the itching in about three weeks.

Dr. Beinhauer's method is much shorter. However, there is a certain amount of danger. I think that the danger in the use of barbiturates is practically nil. Occasionally a patient is allergic, but I have used the method for twenty years and have never had serious difficulty. The patients do sometimes fall, if they are not carefully watched, and injure themselves, but, as far as the drug itself is concerned, I see no harmful effects from rather large doses of the barbiturates.

Dr. Fred M. Jacob, Pittsburgh: Dr. Beinhauer said that a number of patients expressed a lack of enthusiasm for the results. It is a heroic measure, and in some cases heroic patients are necessary.

Sometimes, however, they are in a state of despair. A patient with one of the worst instances of the disease that I have seen was asleep for practically fourteen hours a day for more than ten days, but if her domestic troubles are not alleviated she will have a recurrence.

In reference to case 12 in the table, the patient was a prominent physician, a highstrung busy man. He had many difficulties. During a period of two years his condition could be controlled with moderate doses of barbiturates at night, permitting him to sleep; but the patient reached a point at which it seemed possible that death might occur. He was in such a state of despair that he could not sleep at all. He was given a course of anesthesia. On the chart, Dr. Beinhauer shows that he obtained four hours' relief, but his mental attitude changed and he ceased to be so refractory. He had a prolonged vacation and has been entirely well for the last five years, so that I think that it is one of the most striking results shown on the chart.

DR. LAWRENCE G. BEINHAUER: I wish to thank the members who participated in the discussion of this paper.

This is essentially a preliminary report of treatment which may appear to be heroic but which is sometimes necessary to effect relief. This type of medicament is an anesthetic; therefore I have taken into consideration the potential dangers. I have purposely been conservative in this presentation, realizing that I was dealing with a drug of potential danger.

It is necessary again to emphasize that the medicament should not be used as a first choice but rather as the last choice; it should be used only when recognized therapeutic measures have been exhausted.

The treatment, so far as I have been able to observe, is safe when properly supervised. Relief is afforded, and most patients express a willingness to undergo another course of the treatment if the occasion should arise. Most patients are gratified by the fact that they are able to sleep. The anxiety associated with the condition is greatly eased. I feel that further study in a larger series of cases will better determine the value of this type of treatment.

TREATMENT OF EARLY SYPHILIS WITH SODIUM PENICILLIN

A Preliminary Report with a Comparison of Results with 4,800,000 Units, Administered in Seven and a Half Days, with Smaller Dosages

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IN 1943, soon after the demonstration of the treponemicidal action of penicillin by Mahoney and his co-workers,[1] a nationwide study was organized in order to determine the therapeutic efficacy of penicillin in syphilis. Publications of the cooperative study have presented the results of treatment of early syphilis with total dosages ranging from 60,000 to 2,400,000 units given intramuscularly in divided doses over four to fifteen day periods.[2] The results thus far available indicate that, although penicillin is effective in syphilis, the optimum regimen of treatment has not yet been defined. Investigation has recently been directed toward determining the effect of (*a*) utilizing large total dosages and (*b*) prolonging the duration of treatment. The first of these alternatives is considered in the present paper, which reports

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1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**:355, 1943.

2. (*a*) Moore, J. E.; Mahoney, J. F.; Schwartz, W.; Sternberg, T., and Wood W. B.: The Treatment of Early Syphilis with Penicillin: A Preliminary Report of 1,418 Cases, J. A. M. A. **126**:67 (Sept. 9) 1944. (*b*) The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, ibid. **131**:265 (May 25) 1946. (*c*) The Changing Character of Commercial Penicillin, with Suggestions as to the Use of Penicillin in Syphilis, Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration, ibid. **131**:271 (May 25) 1946.

preliminary results of a schedule employing commercial sodium penicillin in a total dosage of 4,800,000 units in seven and a half days. The results of this schedule are compared with those of smaller dosages given over a similar period of time and previously reported in the cooperative study.

MATERIAL AND METHODS

All of the 123 patients included in this report presented dark field positive lesions of early (primary, secondary or relapsing) syphilis. The distribution of these patients according to race, sex, and diagnosis at the beginning of treatment is indicated in table 1.

There were 31 per cent Negro male patients, 27 per cent Negro female patients, 23 per cent white male patients and 19 per cent white female patients. Of the entire group, for 59 per cent the diagnosis was secondary syphilis, for 22 per cent seropositive primary and for 10

TABLE 1.—*Distribution of* 123 *Patients by Race, Sex and Diagnosis at Beginning of Treatment*

Race (Sex)	Original Patients		Distribution of Original Patients by Stage of Disease (Percentage)				
	No.	Percentage	Seropositive Primary	Seronegative Primary	Secondary	Previously Treated	Total
Negro (M)	39	31	13	28	54	5	100
Negro (F)	33	27	3	3	91	3	100
White (M)	28	23	18	28	36	18	100
White (F)	23	19	4	31	52	13	100
Total	123	100	10	22	59	9	100

per cent seronegative primary. Ninety-one per cent of Negro female patients had secondary syphilis, while only 36 per cent of white male patients had advanced to this stage. The "previously treated" group (9 per cent), so called because of the difficulty in differentiation, includes both patients with relapses following previous treatment (penicillin and/or metal chemotherapy) and patients with presumed reinfections. All patients were hospitalized, commercial sodium penicillin being administered by intramuscular injection in divided doses of 50,000 units each every two hours, day and night, for 96 injections, a total of 4,800,000 units in seven and a half days. Since this schedule was employed between August 1945 and March 1946, the maximum period of follow-up at this time is nineteen months and the minimum just under twelve months.

For the purpose of comparing these with results previously published, both terminology and statistical method are identical with those employed in the cooperative study. The classification of failures in

treatment includes relapses, clinical and/or serologic, and presumed reinfections. Seroresistance is not included as failure in treatment, and no neurorecurrences have thus far been observed.

> The cumulative failure rates have been based on the assumption that a patient examined at any period was under observation at all previous periods and that he was not a failure until actually observed to be so. On this basis a patient might have been a failure before actual discovery but is assumed to have been successful up to that date.[2b]

> In the calculation of the cumulative percentage becoming seronegative, . . . the phrase "becoming seronegative" is not intended to convey the impression of becoming and remaining seronegative, since all cases becoming seronegative in any observation period were excluded from the computations for all subsequent observation periods.[2b]

This modified life-table method of analysis is based on the assumption that the disease in patients not observed during any one period behaved in a similar fashion to the disease in those who were observed.

RESULTS

Treatment Failure.—Of the 123 original patients, in 16 (13 per cent) treatment had been classified as having failed by the end of eleven months of post-treatment observation and in 20 (16.2 per cent) at eighteen months. Recurrent mucocutaneous lesions developed in 18, 3 of whom presented negative results by dark field examination, but accompanied with confirmed significant increases in serologic titer. Serorelapse alone, i.e., confirmed significant increases in titer without mucocutaneous lesions, occurred in 2 patients.

The cumulative treatment failure rates are shown in table 2. As indicated in the last column there is a progressive increase in the cumulative failures to 16.7 per cent through the end of two hundred and eighty days of post-treatment observation. Thereafter the rate remains the same until the beginning of the second year of follow-up, when the occurrence of failure in 2 additional cases in each of the next two periods raises the cumulative rate first to 20.5 and finally to 31.8 per cent at the end of eighteen months. Because of the smaller number of patients under observation, these latter figures are of doubtful quantitative significance.

Comparison of Cumulative Percentage of Treatment Failure.—The results of the schedule employing 4,800,000 units of penicillin in seven and a half days are graphically compared with several schedules employing lesser amounts previously published by the cooperative group.[3] In these graphs, the ordinates represent the cumulative percentages failing (figs. 1 and 2) or becoming seronegative (figs. 3 and 4), and the abscissas record the days after the start of treatment. It

3. Footnotes 2*b* and 2*c*.

should be pointed out that the schedules previously reported are not strictly comparable with our own, since in the present study penicillin was given at two hour rather than three hour intervals. The total duration of treatment was the same (seven to eight days).

The cumulative percentage of patients whose response to treatment was failure by each of three schedules is illustrated in figure 1. At the end of three hundred and eight days of post-treatment observation the cumulative failure rate for a schedule employing 1,200,000 units was approximately 18 per cent; for 2,400,000 units it was 15 per

TABLE 2.—*Cumulative Percentage of Cases in Which Treatment Failed*

Observation Period (Days)	No. of Patients Under Observation at this or Subsequent Period	No. of Cases of Treatment Failure Observed This Period	Cumulative Percentage of Cases of Treatment Failure at End of Periods
0-28	123	0	—
29-56	108	1	0.9
57-84	104	3	3.8
85-112	98	1	4.8
113-140	93	2	6.8
141-168	90	5	12.0
169-196	80	1	13.1
197-224	75	1	14.3
225-252	72	1	15.4
253-280	68	1	16.7
281-308	60	0	16.7
309-336	58	0	16.7
337-364	51	0	16.7
365-456	44	2	20.5*
457-548	14	2	31.8*

*The last two periods were of three months' rather than of twenty-eight days' duration. These cumulative rates are of dubious quantitative significance because of the small number of patients under observation.

cent and for 4,800,000 units it was 17 per cent. These minor differences are not statistically significant.

The comparison shown in figure 2 is included because of the fact, publicized in May 1946, that commercial penicillin had been a changing mixture of at least four different penicillins.[2c] As originally produced (prior to 1944), commercial penicillin apparently contained predominately penicillin G or a combination of penicillins G and F. During 1944, because of changing methods of manufacture, commercial penicillin is thought to have contained increasingly more K and F, particularly the former, at the expense of G. Eagle and Musselman[4]

4. Eagle, H., and Musselman, A.: The Low Therapeutic Activity of Penicillin K Relative to that of Penicillins F, G, and X, and Its Pharmacological Basis, Science **103**:618, 1946.

have since shown that penicillin K is rapidly inactivated by human serum and that after parenteral administration appreciably smaller amounts are excreted in the urine. It has subsequently been reported that K is relatively ineffective in the treatment of experimental syphilis in rabbits.[2c] In addition, there is evidence that penicillin was less

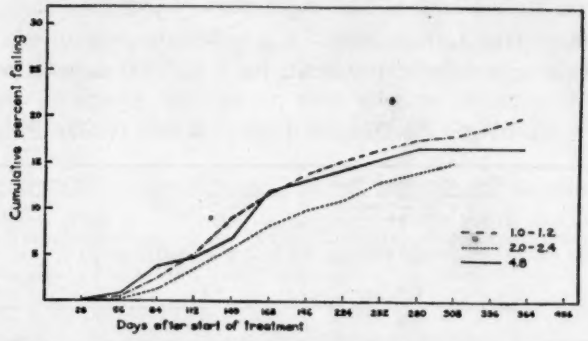

Fig. 1.—Results of treatment in early syphilis with penicillin, showing cumulative rates of failure following treatment with three schedules, 1,200,000, 2,400,000 and 4,800,000 units of penicillin, over a period of seven to eight days. With the 4,800.000 schedule injections were given every two hours; with the others, injections were given every three hours.

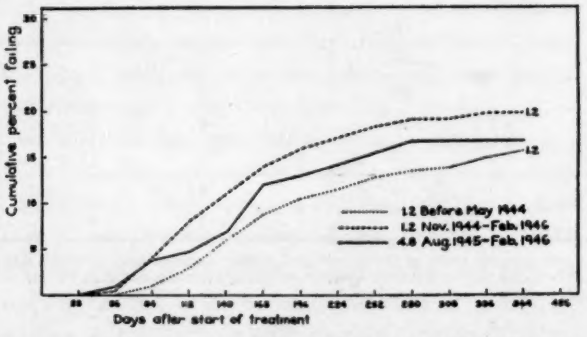

Fig. 2.—Results of treatment of early syphilis with penicillin showing the cumulative rates of failure according to the schedules used and the dates when treatment was started. With the schedule of 4,800,000 units of penicillin, the injections were given every two hours; with the 1,200,000 schedule injections were given every three hours. The duration of treatment was seven to eight days.

efficacious in the treatment of early syphilis in human beings during 1945 than at the outset of the nationwide study (1943-1944).[2c]

Graphs from the cooperative study,[2c] reproduced in figure 2, show the cumulative failure rates with 1,200,000 units of commercial sodium penicillin in seven and a half days as employed prior to May 1944 and the result with the same schedule as used between November 1944 and February 1946. As indicated on the graph, the results obtained in the earlier were better than those during the later period.

The differences were significant statistically. For comparison, our results with four times as much penicillin in the later period have been superimposed. The latter cumulative failure rates fall approximately midway between the smaller schedules and are not significantly different from either.

Comparison of Cumulative Percentage Becoming Seronegative.[5]—Figure 3 compares the cumulative percentage becoming seronegative[5] in the present material with four previously reported schedules—64,000 to 300,000 units, 300,000 to 600,000 units, 1,000,000 to 1,200,000 units and 2,000,000 to 2,400,000 units.[2b] For the first few months the results with the schedule of 4,800,000 units correspond closely to the curve of the smallest total dosage (64,000 to 300,000). After two hundred and fifty-two days of post-treatment observation, the curve rises to maintain a position midway between the 300,000 to 600,000 and 2,000,000 to 2,400,000 schedules but considerably below the 1,000,000 to 1,200,000 schedule.

Figure 4 draws a comparison again between the results of the 4,800,000 schedule as administered between August 1945 and February 1946 and those of 1,200,000 schedule as administered before May 1944 and also from November 1944 to February 1946. Here again the curve representing our results lags during the early months following treatment and finally after two hundred and eighty days approximates that of the 1,200,000 units schedule employed during the same period.

COMMENT

Comparison of Results by Total Dosage.—The cumulative percentage of treatment failures, approximately 17 per cent at the end of eleven months of post-treatment observation, obtained in the treatment of 123 patients with early syphilis by a schedule employing a total of 4,800,000 units of commercial sodium penicillin administered over a period of seven and a half days, suggests that this relatively large dosage may be no more effective than smaller amounts administered during a similar period of time. Data previously reported in the national penicillin study[2b] indicate a progressive decline in the

5. As previously indicated, the phrase "became seronegative" does not mean became and *remained* seronegative. Patients in whom the disease was originally seronegative, e.g., seronegative primary syphilis, are eliminated entirely in this calculation. In addition, in computing the patients under observation during each period, those who have already achieved seronegativity, those observed for the last time but still seropositive and those in whom treatment was already adjudged as having failed are all deleted from the computations for subsequent observation periods. It should be emphasized that all groups are included in the calculations of the cumulative rates of failure.

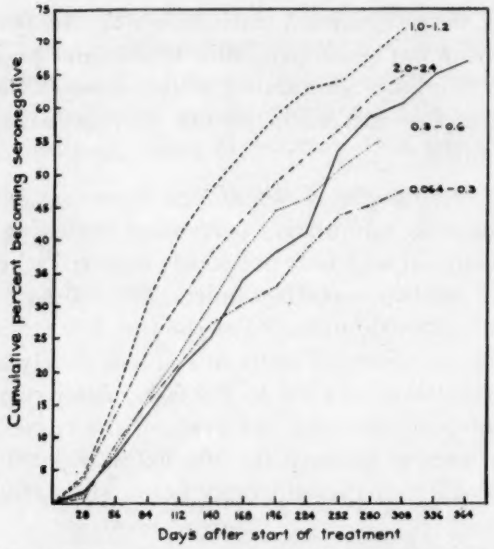

Fig. 3.—Results of treatment of early syphilis showing the cumulative percentage of patients in whom the disease became seronegative, according to the schedules used. The duration of treatment was seven to eight days, with injections given every two hours in the 4,800,000 schedule and every three hours in the other schedules.

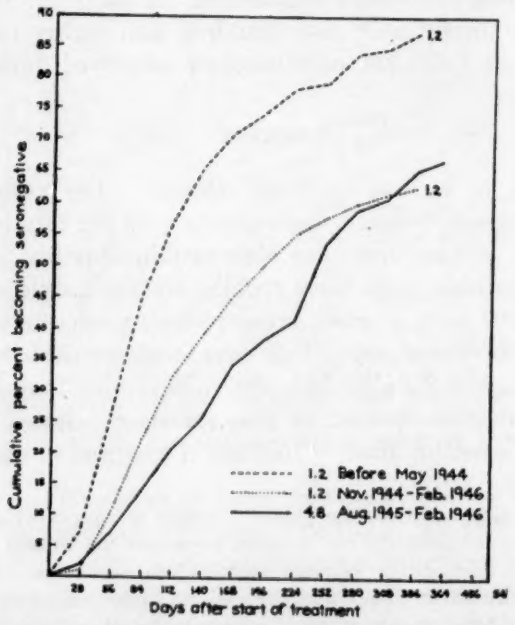

Fig. 4.—Results of treatment of early syphilis, showing the cumulative percentage of patients in whom the disease became seronegative, according to the schedules used and the dates treatment was started. The duration of the treatment was seven to eight days, with injections given every two hours in the 4,800,000 schedule, and every three hours in the 1,200,000 schedule.

cumulative percentage of treatment failures (at the end of eleven months) with increasing total dosage, e.g., 62 per cent failure with 60,000 units total dosage, 42 per cent with 300,000, 26 per cent with 600,000, 18 per cent with 1,200,000 and 15 per cent with 2,400,000. However, with the last two of these schedules the failure rates differ insignificantly, showing that doubling the total dosage over an identical treatment period does not materially affect the results at the end of eleven months. These results and those following a fourfold increase in total dosage herein reported favor the hypothesis that there may be an irreducible minimum below which the failure rate will not fall, regardless of how much more penicillin is given over a similar period of time. In support of this, Eagle and his co-workers[6] have presented evidence that in syphilis in rabbits, at least, very small amounts of penicillin (so minute in fact that penicillin was never present in measurable amounts in the serum) are treponemicidal and that the period over which treatment is administered is all-important. These investigators suggested that with the administration of increasingly large dosages over short periods of time much of the penicillin is wasted and that smaller dosages over longer periods of time may be more effective.

Comparison of Results by Date of Treatment.—The relative proportions of the four known penicillins contained in commercial sodium penicillin during the period of time included in the present study are not known. It is believed that refinements in production methods were accompanied both with relative increases in the amounts of penicillin K (a therapeutically less effective penicillin) and with reductions in "impurities" (some of which have been shown to exert treponemicidal action[7]). These changes in the characteristics of commercial sodium penicillin are thought to account, in part at least, for its reduction in effectiveness in early syphilis in human beings during the period November 1944 to February 1946 as compared to the period prior to May 1944. The results of the present study, as illustrated in figures 2 and 4, fail to demonstrate significant differences between the therapeutic efficacy of 4,800,000 units of commercial sodium penicillin and that of 1,200,000 units (a fourfold difference), when compared with the latter as administered either originally or more recently over a similar period of time. It would seem unlikely that the changing character of penicillin can account entirely for the

6. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, Bull. Johns Hopkins Hosp. **74**:168, 1946.

7. Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **29**:214, 1945.

apparent lack of superior therapeutic results with the larger schedule. These clinical results lend further credence to the theory advanced by Eagle that prolongation of treatment rather than intensification may be the desideratum for syphilis.

In drawing comparisons between the results of different methods of treatment for early syphilis, at least five factors must be taken into consideration: (*a*) the composition of the original material in respect to the duration of infection, (*b*) the efficiency of follow-up and the potential follow-up period, (*c*) the effect of the changing composition of the material from period to period in respect to the duration of infection, (*d*) the proportion of relapses and reinfections in patients classified as having failed to be cured by treatment and (*e*) in comparisons of serologic response, the sensitivities of the serologic tests performed.

Composition of Original Material in Respect to Duration of Infection.—There is evidence that, both with metal chemotherapy[8] and with penicillin therapy[2b] of early syphilis, the outcome of treatment, other factors being comparable, is directly related to the duration of disease at the beginning of treatment. Cumulative failure rates under similar conditions of treatment, have been shown to be significantly higher when treatment is begun after secondary lesions have appeared than when started earlier.

The stage of the disease at the start of treatment in the 123 patients included in this study was shown in table 1 to be as follows: secondary syphilis 59 per cent, seropositive primary 22 per cent and seronegative primary 10 per cent.[9] This information was not available in the published reports of the schedules with which the present one is compared, and, therefore, the effect of differences in such distribution cannot be assessed. Because the total number of patients in the present series is small, the cumulative failure rate for secondary syphilis considered alone (16.2 per cent at the end of eleven months) [10] does not differ significantly from that for all stages combined.

The Efficiency of Follow-Up and the Potential Follow-Up Period.—It has been demonstrated that cumulative failure rates with identical schedules of treatment are higher in clinics maintaining good follow-up records than in those with poorer ones.[11] In the material

8. Eagle, H.: The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen: A Preliminary Analysis of the Results in the First 4,823 Cases, J.A.M.A. **126**:538 (Oct. 28) 1944.

9. Nine per cent were classified as previously treated (mentioned earlier in the text).

10. Table not included.

11. Report of Central Statistical Unit, National Penicillin in Syphilis Study, Washington Conference, April 17, 1947.

with which the present data are compared, only 20 per cent of the total number of patients treated were under observation by the end of eleven months after treatment. "This decrease is the result both of the constant accretion of new cases and the loss of patients who could have been followed for a given period but were not."[2b] Our patients could have been followed up for a minimum of eleven months, and 54.6 per cent were still under observation at the end of that time. The follow-up ratings[12] for clinics contributing to the larger study varied from 1 per cent to 75 per cent at eighteen months; for the Syphilis Clinic of the Washington University Clinics it was 64 per cent at this time. For the computation of these percentages, failures considered as having been completely followed up.

The Effect of the Changing Composition of the Material from Period to Period in Respect to Duration of Infection.—Since the efficacy of treatment is related to the time of its administration, it is possible that the distribution of patients by duration of disease, who are under observation during any one period of time, may materially affect the calculated failure rates for this and for subsequent periods. If patients who are lost from observation are predominantly those with syphilis of short duration, failure rates will tend to be those for syphilis of longer duration. Specific rates of stage or duration will obviate this difficulty. Such specific rates will mean little in a series as small as the present one. Therefore, other descriptive data should be utilized to take these differences into account. Since persons in certain racial and sex groups are frequently seen clinically for the first time in later stages of early syphilis than others, and since in certain groups persons respond more readily to follow-up efforts, differences in race and sex distribution in subsequent periods may also be important. An analysis of the sex and race distribution by diagnosis at the beginning of treatment is shown in table 3 for those patients of this study who were under observation at the end of eleven months.

An examination of the percentages in tables 1 and 3 shows them to be strikingly similar, indicating that the total losses[13] (by failure or otherwise) in each race, sex and diagnostic group were fairly constant. The validity of comparisons of cumulative failure rates depends not only on original similar composition of the material by race, sex and duration but also on similar changes in this composition. In the present material there was little change in composition. This may be an important factor in comparisons, provided that the ratios of failures

12. These ratings include patients on all schedules.

13. Losses in the sense that they are considered no longer under observation (both failures and follow-up losses).

to total losses[13] are similar in the data being compared. In this material these ratios are shown in table 4. In spite of the similarity in distribution at the beginning and at the end of eleven months, there is no constancy in these ratios. Among Negroes the ratio of

TABLE 3.—*Distribution of 51 Patients by Race, Sex and Diagnosis Remaining Under Observation at the End of Eleven Months*

Original Patients Still Under Observation at 11 Months

Race (Sex)	Distribution by Stage of Disease at Time of Treatment (Percentage)						Total
	No. of Patients	Percentage	Seronegative Primary	Seropositive Primary	Secondary	Previously Treated	
Negro (M)	16	31	12.5	25	50	12.5	100
Negro (F)	14	27	7	0	86	7	100
White (M)	10	20	20	20	40	20	100
White (F)	11	22	9	18	73	0	100
Total	51	100	12	15	63	10	100

failures to total losses is significantly higher than that among white persons (31 per cent and 10 per cent). In respect to the stage of disease, the ratio of failures to total losses is not significantly higher

TABLE 4.—*Ratio of Losses Due to Failure of Treatment to Total Losses*

	Number Lost by Failure Plus Follow-up Losses	Failure (No. of Patients)	Ratio of Failures to Total Losses (Percentage)
Negro (M)	23	6	26.1
Negro (F)	19	7	36.8
Negroes	42	13	31.0
White (M)	18	1	5.6
White (F)	12	2	16.7
White patients	30	3	10.0
Total	72	16	22.2
Primary seronegative	6	2	33.3
Primary seropositive	19	5	26.3
All primary	25	7	28.0
Secondary	41	9	21.9

among patients with primary than among those with secondary syphilis (28 per cent and 21.9 per cent).

Similar data for the material with which these results are compared are not available to us. Similarity in changing composition and

failure-loss ratios would materially add to the validity of the comparisons.

Treatment Failure, Proportion of Relapses and of Reinfections.—The differentiation of relapse from reinfection or superinfection constitutes a problem difficult, if not impossible, of solution in the light of present day information. No unanimity of opinion exists as to the criteria acceptable for the differentiation of these phenomena. On the one hand, while reinfection may indicate cure of the initial infection, relapse certainly denotes failure. The national penicillin study has adopted, until more information is available, the only valid solution of this dilemma, namely classifying the results in all patients in whom recurrent lesions developed as treatment failures. Nonetheless, the extent to which the classification as treatment failure is weighted with reinfections is a major consideration in comparisons such as these. It is theoretically possible for a "perfect" schedule of treatment to have (under the present system of classification) as high a rate of "failure" (all reinfections) as a grossly imperfect one (predominantly relapses and superinfections). For the schedules herein compared, the proportions of the failures classified as reinfections by the cooperating clinics, based on clinical and epidemiologic evidence, was listed as follows: 1,200,000 units, 115 failures, 9.5 per cent supposed reinfections; 2,400,000 units, 90 failures, 10 per cent supposed reinfections; and 4,800,000 units, 20 failures, 20 per cent supposed reinfections.

TABLE 5.—*Proportion of Cases in Which Failure Was Classified as Reinfection*

Dosage (Units of Penicillin)	Failure (No. of Cases)	Supposed Reinfection (Percentage)
1,200,000	115	9.5
2,400,000	90	10
4,800,000	20	20

Two possible approaches to the solution of this difficulty present themselves. The first is a comparison of failure rates under similar treatment schedules employed in different geographic locations: those of known high incidence of infection and those of known low incidence of infection. Such comparisons must take into account stage, race and sex differences, socioeconomic status and known habits and customs of the populations involved.

The second involves detailed epidemiologic study of all patients treated with respect to their sexual habits and the periodic examination of both pretreatment and post-treatment contacts.

Comparisons of Serologic Response.—In figures 3 and 4 the cumulative percentage of patients becoming seronegative following treatment by the present schedule appears to lag behind the curves of smaller total dosages. The multiplicity of factors which render difficult comparisons of serologic response following treatment for early syphilis have been recently emphasized elsewhere[14] and will not be given detailed consideration here. The most likely explanation of these seemingly paradoxic results is that the quantitative technic employed in our own laboratory is more sensitive than the over-all sensitivity of the multitude of tests performed in the cooperating clinics of the national study. If this assumption is true, and we have other reasons for believing that it may be, the interval between treatment and the attainment of seronegativity for our own material would tend to be prolonged.

The total influence of these five factors on the comparisons of the results of the present schedule with those previously reported cannot be evaluated with the data now available. It is to be emphasized, however, that the validity of these and of other similar comparisons is conditional on the homogeneity of the material in these fundamental respects.

SUMMARY

The preliminary results of treatment of 123 patients with early syphilis by a schedule employing 4,800,000 units of commercial sodium penicillin over a seven and a half day period are reported. These results are compared with those previously published by the national penicillin study which utilized smaller dosages over a similar period of time (but with a longer interval between injections—three hours rather than two hours).

In the present material the cumulative percentage of treatment failures (16.7 per cent at the end of eleven months) does not differ significantly from the results previously obtained elsewhere with either 1,200,000 or 2,400,000 units.

Comparisons of results by date of treatment, included because of the implications of the changing character of commercial penicillin, revealed no significant differences between the results of the present schedule (4,800,000 units), used between August 1945 and February 1946, and those obtained with 1,200,000 units, as employed either before May 1944 or from November 1944 to February 1946.

The results in this series of patients suggest that increasingly large dosages of commercial penicillin may not be superior to smaller dosages administered over similar short periods of time.

The necessity for cautious interpretation of comparisons of small series of patients is emphasized. Important considerations in such comparisons include (*a*) the composition of the original material in respect to duration of infection, (*b*) the efficiency of follow-up, (*c*) the effect of the changing composition of the material during post-treatment observation in respect to duration of infection, (*d*) the proportion of relapses and of reinfections in the patients classified as failing to be cured by treatment and (*e*) in comparisons of serologic response, the sensitivities of the serologic tests performed.

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14. Clark, E. G.; Maxwell, R. W., and Scott, V.: The Serologic Response Following Penicillin Therapy for Early Syphilis, Am.J.M.Sc. **213**:535, 1947.

Clinical Notes

BASAL CELL CARCINOMA OF SWEAT GLAND ORIGIN
Report of a Case

HARRY L. ARNOLD JR., M.D., HONOLULU, TERRITORY OF HAWAII

The concept of adnexal carcinoma of the skin, as developed by Foot,[1] has given an integrated explanation of the basal cell carinoma which accounts for its distribution, its variety of cellular patterns and its infiltrative—but never metastasizing—habits of growth. The origin of basal cell carcinoma from sweat gland ducts has been recorded, but both Foot and Gates, Warren and Warvi[2] regarded its origin from sweat gland acini as extremely rare, if not actually unknown.

The expression "origin (of a neoplasm) from (a tissue or structure)" will bear a little explanation. It is commonplace that malignant neoplasms, like benign ones, may exhibit what has been called "homotypic," as opposed to "heterotypic," structure, that is, they may tend to reproduce a normal pattern. It is then commonly assumed that they have arisen in, or have been derived from, a normal cell (or tissue) exhibiting this same pattern.

While this assumption is no doubt usually founded on fact, it is not necessarily so; there is no reason why such a neoplasm could not have arisen in a pluripotential cell which—while capable of producing such a normal cellular pattern, and perhaps destined ultimately to do so—had not yet become so fully differentiated. In such circumstances the assumption that the neoplasm in question had had its "origin from" the imitated normal structure would not be exactly a correct one.

It is plain that this argument—except perhaps in the most extraordinary circumstances—is mere quibbling. It is offered in extenuation of the view that "presenting structural resemblance to" may be taken as tantamount to "having its origin in." It is also offered to make it clear that the lesion to be reported here could not be proved to have originated in a sweat gland cell; it could have, conceivably, had its origin in a basal cell of the epidermis which, under some stimulus, not only became neoplastic but also differentiated along the lines of sweat gland acinus cells.

Dr. Tilden and I feel, then—and Shields Warren,[3] who examined sections of the lesion, also believes—that the vacuolated lipid-free cells comprising the neoplasm reported here must be interpreted, for want of a better explanation, as of sweat gland acinus origin. The clinical appearance of the lesion, its coherently infiltrative habit of growth and its microscopic architecture all indicate clearly that it is in fact a basal cell carcinoma, or "adnexal carcinoma," of the skin. The clinical appearance was so characteristic, indeed, that the desirability of a preoperative photograph did not occur to me.

1. Foot, N. C.: Adnexal Carcinoma of the Skin, Am. J. Path. **23**:1 (Jan.) 1947.
2. Gates, O.; Warren S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591 (July) 1943.
3. Warren, S.: Personal communication to the author.

REPORT OF A CASE

A. W., a 52 year old registered nurse, was first seen in May 1946, being referred by Dr. Samuel R. Wallis of Lihue, Kauai, Territory of Hawaii, because of an enlarging tumor of the skin of the right side of the nose. This had first been noted approximately eleven years previously; in 1945, a dermatologist in New York had made a clinical diagnosis of basal cell carcinoma and had treated it with roentgen rays (1200 r). It had not responded to this, and indeed, had grown more rapidly after the treatment than it had done previously.

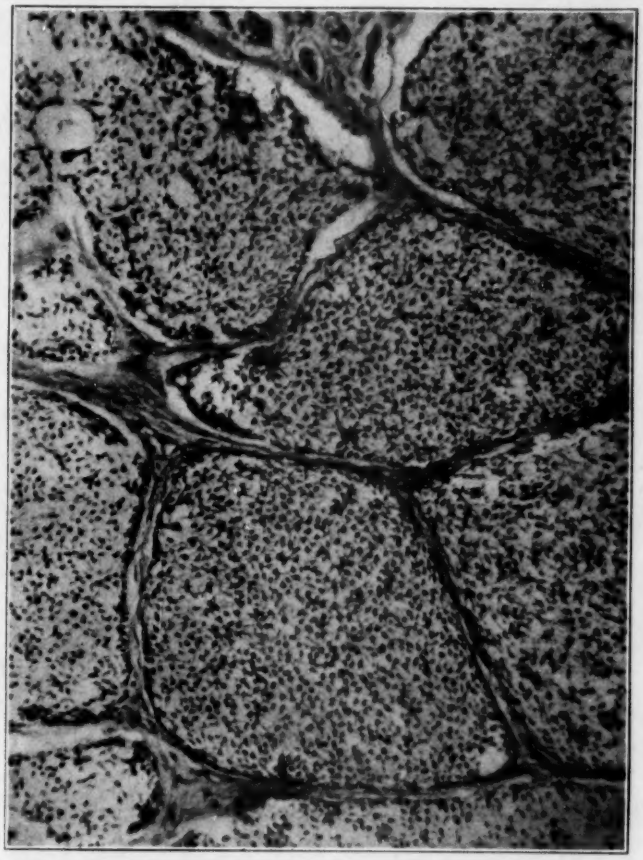

Fig. 1.—Closely packed sharply outlined medullary masses of neoplastic cells, showing the microscopic architecture of basal cell carcinoma (hematoxylin and eosin × 130).

At the time of this examination, the patient was noted to be of sandy complexion and appeared somewhat younger than her stated age; her skin was moderately freckled, but relatively free of nevi, and no keratoses were seen. On the right side of the nose, about 1.5 cm. proximal to its tip, was an oval translucent-looking plaque, elevated about 2 mm. above the surrounding skin and measuring about 7 by 10 mm. The skin covering it was smooth and seemed somewhat atrophic.

Under local infiltration with procaine hydrochloride, the lesion was shelled out with a semisharp ring curet; it came away easily in one large spheroidal piece, nearly as deep as it was broad; an astonishingly deep crater was left in the normal tissue of the nose. After that had been vigorously curetted, without grossly removing any more tissue, it was thoroughly cauterized with the galvanic cautery, in order to produce hemostasis and destroy remaining neoplastic cells. No dressing was applied; the defect was left to heal under the hemorrhagic crust that subsequently formed. The operative site was then irradiated and a 4 mm. margin of

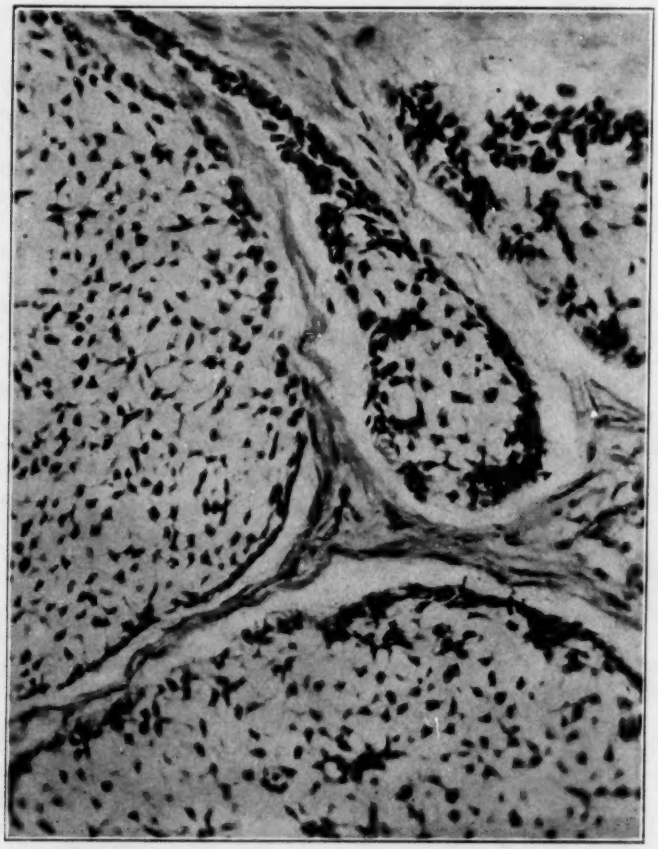

Fig. 2.—Pyknotic stellate nuclei and abundant vacuolated cytoplasm of neoplastic cells, in which no lipid material could be demonstrated (hematoxylin and eosin × 300).

surrounding normal skin, with the following factors: 80 kilovolts peak, 5 milliamperes, 21 cm. anode-skin distance, 0.5 mm. aluminum filtration, half-value layer 1.5 mm. of aluminum, dose 500 r, three treatments, five days apart, a total dose of 1500 r.

The routine frozen sections of the removed tissue presented a remarkable picture, subsequently confirmed in paraffin sections. The corium was largely replaced by almost contiguous oval nests of cells, presenting exactly the appearance —under moderate magnification and inexact focusing—of an ordinary "medullary"

type of basal cell carcinoma (fig. 1). The individual cells comprising the nests presented, however, a surprising appearance. Their nuclei were small and pyknotic and often somewhat stellate in outline. They had abundant cytoplasm, made up almost entirely of vacuoles of variable size (fig. 2). Their resemblance to ordinary sebaceous gland cells was so exact that several weeks elapsed before sudan III stains were made on frozen sections in order to "confirm" (as was thought) the presence of sebaceous, or at least lipid, material. No such substance was demonstrated.

Two months later, the patient returned with an apparent recurrence of residual carcinoma in the operative site, which had completely healed. A second curettement and cauterization were performed, removing only a small amount of tissue. The tissue on this occasion presented a normal-looking epidermis and a few nests of atypical epithelial pearls, which were not regarded as of diagnostic value. No cells of the type seen in the original neoplasm were observed. Despite the clinical appearance of recurrent neoplasm, it was felt that proof of the occurrence of this was lacking and that the picture might have been produced by aberrant epithelial growth incident to healing.

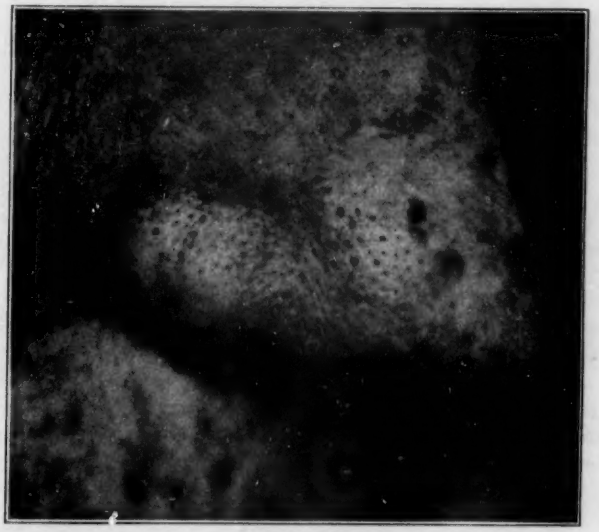

Fig. 3.—The final scar.

The defect produced by this second operation healed rapidly and reasonably well, leaving at the time of writing (May 1947) a moderately depressed atrophic scar, with which the patient was pleased (fig. 3).

COMMENT

It should be made clear that this lesion does not correspond to an adenocarcinoma of sweat gland origin. Such a lesion is properly called a hidradenocarcinoma or a hidradenoid carcinoma and should be classified with the adenocarcinomas, for it is—unlike the lesion here reported—capable of metastasis. Reference should be made to Gates, Warren and Warvi's review of sweat gland tumors[2] for a full discussion of adenocarcinoma of sweat gland origin.

SUMMARY AND CONCLUSIONS

A lesion is described which, in gross appearance, coherent medullary and infiltrative growth pattern and microscopic architecture, is a typical basal cell carcinoma and in which the individual cells, though they closely resemble sebaceous gland cells, contain no demonstrable lipid material.

The case is reported as a rare instance of basal cell carcinoma of the skin, in which the cell type appears to be the sweat gland acinus cell.

NOTE—As of July 1948 there had been no apparent recurrence.

ACKNOWLEDGMENTS

Dr. Irvin L. Tilden, of the Department of Pathology of The Clinic, Honolulu, made the photomicrographs and the clinical photograph, and collaborated in the interpretation of the histologic sections.

Dr. Shields Warren, of Boston, examined sections of the lesion and originally suggested the diagnosis of sweat gland carcinoma.

881 South Hotel Street.

TRAUMATIC ATROPHY OF THE SUBCUTANEOUS FAT DUE TO USE OF A PNEUMATIC DRILL

Report of a Case

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A review of the literature reveals a number of reports of vascular damage from the small pneumatic hammers used in mines for cutting stone.[1] These hammers operate at a rate of about 3,000 strokes per minute. Similar changes have not been observed from the iron worker's hammer, operating at 1,500 strokes per minute. No references were found to atrophy of fat due to the use of the larger pneumatic drill, used in construction work to break up cement and rock. These drills operate at a rate of from 1,000 to 1,500 strokes per minute.

REPORT OF A CASE

A 21 year old white man was hospitalized for observation of previously treated schistosomiasis japonica. He was referred to the dermatology service for a "butterfly-shaped lesion of the anterior aspect of the abdominal wall."

Examination of the skin revealed two oval lesions, each 5.4 by 6.0 cm. in diameter, located in the mesogastrium and centered over the lateral border of the rectus muscle. The lesion on the right was located slightly cephalad to that on the left. The lesions consisted of depressions of the skin of about 3 mm., with smooth sloping borders (figure). These areas showed prominence of the venules and veins

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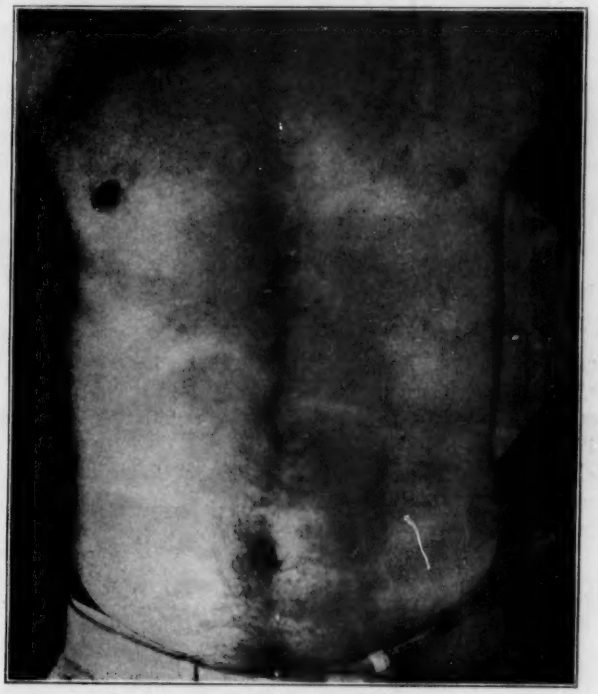
1. Hardgrove, M. A. F., and Barker, N. W.: Pneumatic Hammer Disease: Vasopathic Disturbance of Hands in Stone-Cutters, Proc. Staff Meet., Mayo Clin. **8**:345 (June 7) 1933.

of the subcutaneous tissue and, therefore, had a slightly darker color. The epidermis appeared normal, and the hair follicles were not atrophic. Sensation in the involved areas was intact to pain, touch and temperature.

Occupational history revealed that the patient had occasionally used a pneumatic drill as a plumber's apprentice from July 1942 until June 1943. During that period he spent an estimated total of two hundred and fifty hours using that equipment. He stated that since he was rather light, he leaned heavily on the rounded top of the pneumatic drill to increase its action. He was inducted into an engineer construction battalion in June 1943. From Nov. 15, 1944 until Dec. 15 he operated a large pneumatic drill continuously for eight or more hours daily in a combat construction assignment, with a total of at least two hundred and



Photograph of the patient, showing the depressed areas.

forty hours over a thirty day period. He also stated that he alternated positions, placing the right foot forward and applying the dome of the apparatus to the right side of the abdomen half the time and placing the left foot forward and applying the apparatus to the left side of the abdomen for the remainder of the time.

The general physical examination showed no abnormalities. The erythrocyte count was 4,290,000 per cubic millimeter, hemoglobin 84 per cent and the leukocyte count 5,450 per cubic millimeter. The differential leukocyte count showed 50 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 5 per cent monocytes and 13 per cent eosinophil leukocytes. Urinalysis showed no abnormalities. The reaction to the Kahn test was negative.

Histologic examination showed a normal epidermis. There was definite, though moderate, fragmentation of the collagen fibers in the lower aspect of the corium. The subcutaneous fat cells were uniformly small and contained a reduced fat content, with a relative increase in nuclei.

COMMENT

The condition in the case reported was undoubtedly due to the repeated vibratory impact of the rounded dome of a pneumatic drill to the involved areas of skin, and the pathologic changes were minor except for decrease in the fat content of the subcutaneous fat cells. Subcutaneous fat necrosis and panniculitis can be eliminated from differential diagnoses, since there was no evidence of necrosis or inflammation either clinically or histologically.

No reference to a similar condition was found in standard texts of dermatology,[2] occupational disease of the skin[3] or a recent discussion of occupational stigmas.[4]

Significant factors in the production of this condition could appear to be: (1) that the patient had much more continuous exposure to this peculiar type of trauma under combat conditions than would be likely in civilian work and (2) that, because of his size and weight, he applied the dome of the instrument directly to the abdominal wall, whereas the usual method of a larger and heavier operator is to carry the major vibratory impact with the braced arms, with the hands applied to the handles.

10515 Carnegie Avenue (6).

2. Ormsby, O. S., and Montgomery, H.: Disease of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

3. Schwartz, L., and Tulipan, L.: A Text-Book of Occupational Diseases of the Skin, ed. 1, Philadelphia, Lea & Febiger, 1939.

4. Ronchese, F.: Calluses, Cicatrices and Other Stigmas as Aid to Personal Identification, J. A. M. A. **128**:925 (July 28) 1945.

CONTACT DERMATITIS FROM THE TOPICAL APPLICATION OF STREPTOMYCIN OINTMENT

Report of a Case

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Contact dermatitis from the topical application of streptomycin ointment has not yet been reported. This type of treatment with streptomycin is not employed extensively at the present time. Sulzberger and Baer[1] have used streptomycin topically in otitis externa and cutaneous infections due to Pseudomonas aeruginosa and colon bacilli. Preliminary trials with ointment containing streptomycin in

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Streptomycin and penicillin-streptomycin ointments were supplied by the Bristol Laboratories, Inc.

1. Sulzberger, M. B., and Baer, R. A.: The 1946 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1947, p. 15.

some 70 patients with a variety of dermatoses have elicited no evidence of dermatitis. Preliminary trials with attempts at the induction of eczematous hypersensitization with streptomycin have also been without results. A few patients had been treated with ointments containing penicillin and streptomycin. In 1 case eczematous dermatitis developed and was proved to be due to the streptomycin.

REPORT OF A CASE

A 69 year old white woman was admitted to the Service of Dermatology, Cincinnati General Hospital, because of severe superficial ulcerations and cellulitis of both lower extremities. These lesions were superimposed on bilateral stasis dermatitis. The patient had had previous fractures of the left femur and both ankles. Her serologic reactions of the blood were positive in 1935 and 1942. During the past four years she has experienced shooting pains in the legs and difficulty in walking and has been incontinent of urine and feces.

Photograph showing reactions to patch tests with streptomycin, both in ointment (*C*) and in solution (*A*). The two negative reactions are to penicillin ointment (*B*) and solution (*D*).

The lower part of the legs, from the region of the ankles to the knees, were erythematous and edematous. In addition there were secondarily infected erosions and superficial ulcerations. The general examination revealed typical observations of neurosyphilis with tabes dorsalis.

The laboratory examination revealed a positive Kahn reaction. The Wassermann reaction of the spinal fluid was also positive in dilutions of 0.1 cc., 0.25 cc., 0.50 cc. and 1.0 cc. The colloidal gold curve was 2224422100. The hemoglobin was 12.5 Gm., and the white blood cell count was 6,200.

After four days of treatment with continuous wet dressings with diluted solution of aluminum acetate and elevation of the legs, some secondary infection was still present. Streptomycin ointment was then used on one leg, and, as a comparative study, a combination of penicillin and streptomycin ointment was used on the other. These ointments contained 5,000 units of streptomycin phosphate per gram and 1,000 units of calcium penicillin per gram. The infection subsided;

however, on the twelfth day there appeared acute erythematous vesicular and exudative dermatitis, which involved the areas of both legs to which the ointment had been applied.

Patch tests were performed on the inner aspect of the right arm with the following substances: (1) streptomycin ointment containing 5,000 units per gram, (2) streptomycin solution, 1,000 micrograms per cubic centimeter, (3) penicillin ointment, 500 units per gram, and (4) penicillin solution, 2,000 units per cubic centimeter. At the end of forty-eight hours, the tests to both the streptomycin ointment and solution revealed reactions characterized by erythema and eczematization, which extended beyond the area of contact with these substances. The reactions to both patch tests with penicillin were negative.

SUMMARY

A case of contact dermatitis of the lower extremities due to streptomycin ointment used topically is described. The reactions to patch tests with streptomycin were positive.

A SUGGESTIVE SIGN OF ALLERGY

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For some years, Dr. Charles C. Dennie has called to the attention of his students and associates a sign which he has observed to be rather pathognomonic in most cases of allergy (especially in persons with a history of eczema, hay fever and asthma). This sign is a definite wrinkle just beneath the margin of the lower lid of both eyes, which usually is present at birth or shortly thereafter. It is retained throughout life.

The wrinkle beneath the lower eyelids, a suggestive sign of allergy, in an adult and in an infant.

The accompanying photographs well illustrate this wrinkle in both a man with a history of atopic dermatitis and an 8 month old infant with eczema.

To my knowledge no one has mentioned this suggestive sign in any previous medical literature.

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